

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
19 July 2001 (19.07.2001)

PCT

(10) International Publication Number
WO 01/51673 A2

(51) International Patent Classification⁷: C12Q 1/70,
G01N 33/53, A61K 38/00, 39/21

(21) International Application Number: PCT/US00/35727

(22) International Filing Date: 5 July 2000 (05.07.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/350,841 9 July 1999 (09.07.1999) US

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(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ,
DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

WO 01/51673 A2

(54) Title: METHODS AND COMPOSITIONS FOR INHIBITION OF MEMBRANE FUSION-ASSOCIATED EVENTS, IN-
CLUDING HIV TRANSMISSION

(57) Abstract: The present invention relates to peptides which exhibit potent anti-retroviral activity. The peptides of the invention comprise DP178 (SEQ ID:1) peptide corresponding to amino acids 638 to 673 of the HIV-1_{LAI} gp41 protein, and fragments, analogs and homologs of DP178. The invention further relates to the uses of such peptides as inhibitory of human and non-human retroviral, especially HIV, transmission to uninfected cells.

METHODS AND COMPOSITIONS FOR INHIBITION OF MEMBRANE
FUSION-ASSOCIATED EVENTS, INCLUDING HIV TRANSMISSION

5

1. INTRODUCTION

The present invention relates, first, to DP178 (SEQ ID NO:1), a peptide, also referred to herein as T20, corresponding to amino acids 638 to 673 of the HIV-1_{LAI} transmembrane protein (TM) gp41, and portions
10 or analogs of DP178 (SEQ ID NO:1), which exhibit anti-membrane fusion capability, antiviral activity, such as the ability to inhibit HIV transmission to uninfected CD-4⁺ cells, or an ability to modulate intracellular processes involving coiled-coil peptide
15 structures. The present invention also relates to peptides analogous to DP107 (SEQ ID NO:25), a peptide, which is also referred to herein as T21, corresponding to amino acids 558 to 595 of the HIV-1_{LAI} transmembrane protein (TM) gp41, having amino acid sequences present
20 in other viruses, such as enveloped viruses, and/or other organisms, and further relates to the uses of such peptides. These peptides exhibit anti-membrane fusion capability, antiviral activity, or the ability to modulate intracellular processes involving coiled-coil peptide structures.
25

The gp41 region from which DP107 is derived is referred to herein as HR1. The gp41 region from which DP178 is derived is referred to herein as HR2. As discussed herein, the gp41 HR1 and HR2 regions interact (non-covalently) with each other and/or with
30

T20 and T21 peptides. This interaction is required for normal infectivity of HIV.

The present invention therefore additionally relates to methods for identifying compounds, including small molecule compounds, that disrupt the interaction between DP178 and DP107, and/or between DP107-like and DP178-like peptides. In one embodiment, such methods relate to identification and utilization of modified DP178, DP178-like, DP107 and DP107-like peptides and peptide pairs that interact with each other at a lower affinity than the affinity exhibited by corresponding "parent" or "native" peptides. Further, the invention relates to the use of DP178, DP178 portions, DP107, DP017 portions and/or analogs and other modulators, including small molecules modulators, of DP178/DP107, DP178-like/DP107-like, or HR1/HR2 interactions as antifusogenic or antiviral compounds or as inhibitors of intracellular events involving coiled-coil peptide structures. The invention is demonstrated, first, by way of an Example wherein DP178 (SEQ ID:1), and a peptide whose sequence is homologous to DP178 are each shown to be potent, non-cytotoxic inhibitors of HIV-1 transfer to uninfected CD-4⁺ cells. The invention is further demonstrated by Examples wherein peptides having structural and/or amino acid motif similarity to DP107 and DP178 are identified in a variety of viral and nonviral organisms, and in examples wherein a number of such identified peptides derived from several different viral systems are demonstrated to exhibit antiviral activity. The invention is still further demonstrated by way of Examples wherein other DP178-like and DP107-like peptides are identified that

interact with their corresponding HR1 and HR2 domains with a lower affinity than the affinity exhibited by the native DP178 or DP107 peptide from which they are derived.

5

2. BACKGROUND OF THE INVENTION

2.1 MEMBRANE FUSION EVENTS

Membrane fusion is a ubiquitous cell biological process (for a review, see White, J.M., 1992, Science 258:917-924). Fusion events which mediate cellular
10 housekeeping functions, such as endocytosis, constitutive secretion, and recycling of membrane components, occur continuously in all eukaryotic cells.

Additional fusion events occur in specialized
15 cells. Intracellularly, for example, fusion events are involved in such processes as occur in regulated exocytosis of hormones, enzymes and neurotransmitters. Intercellularly, such fusion events feature prominently in, for example, sperm-egg fusion and myoblast fusion.

20

Fusion events are also associated with disease states. For example, fusion events are involved in the formation of giant cells during inflammatory reactions, the entry of all enveloped viruses into cells, and, in the case of human immunodeficiency
25 virus (HIV), for example, are responsible for the virally induced cell-cell fusion which leads to cell death.

2.2. THE HUMAN IMMUNODEFICIENCY VIRUS

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The human immunodeficiency virus (HIV) has been implicated as the primary cause of the slowly

degenerative immune system disease termed acquired immune deficiency syndrome (AIDS) (Barre-Sinoussi, F. et al., 1983, Science 220:868-870; Gallo, R. et al., 1984, Science 224:500-503). There are at least two distinct types of HIV: HIV-1 (Barre-Sinoussi, F. et al., 1983, Science 220:868-870; Gallo R. et al., 1984, Science 224:500-503) and HIV-2 (Clavel, F. et al., 1986, Science 233:343-346; Guyader, M. et al., 1987, Nature 326:662-669). Further, a large amount of genetic heterogeneity exists within populations of each of these types. Infection of human CD-4⁺ T-lymphocytes with an HIV virus leads to depletion of the cell type and eventually to opportunistic infections, neurological dysfunctions, neoplastic growth, and ultimately death.

HIV is a member of the lentivirus family of retroviruses (Teich, N. et al., 1984, RNA Tumor Viruses, Weiss, R. et al., eds., CSH-Press, pp. 949-956). Retroviruses are small enveloped viruses that contain a diploid, single-stranded RNA genome, and replicate via a DNA intermediate produced by a virally-encoded reverse transcriptase, an RNA-dependent DNA polymerase (Varmus, H., 1988, Science 240:1427-1439). Other retroviruses include, for example, oncogenic viruses such as human T-cell leukemia viruses (HTLV-I, -II, -III), and feline leukemia virus.

The HIV viral particle consists of a viral core, composed of capsid proteins, that contains the viral RNA genome and those enzymes required for early replicative events. Myristylated Gag protein forms an outer viral shell around the viral core, which is, in turn, surrounded by a lipid membrane enveloped derived

from the infected cell membrane. The HIV enveloped surface glycoproteins are synthesized as a single 160 Kd precursor protein which is cleaved by a cellular protease during viral budding into two glycoproteins, gp41 and gp120. gp41 is a transmembrane protein and
5 gp120 is an extracellular protein which remains non-covalently associated with gp41, possibly in a trimeric or multimeric form (Hammariskjold, M. and Rekosh, D., 1989, Biochem. Biophys. Acta 989:269-280).

HIV is targeted to CD-4⁺ cells because the CD-4
10 cell surface protein acts as the cellular receptor for the HIV-1 virus (Dalglish, A. et al., 1984, Nature 312:763-767; Klatzmann et al., 1984, Nature 312:767-768; Maddon et al., 1986, Cell 47:333-348). Viral entry into cells is dependent upon gp120 binding the cellular CD-4⁺ receptor molecules (McDougal, J.S. et al.,
15 al., 1986, Science 231:382-385; Maddon, P.J. et al., 1986, Cell 47:333-348) and thus explains HIV's tropism for CD-4⁺ cells, while gp41 anchors the enveloped glycoprotein complex in the viral membrane.

20 2.3. HIV TREATMENT

HIV infection is pandemic and HIV associated diseases represent a major world health problem. Although considerable effort is being put into the successful design of effective therapeutics, currently
25 no curative anti-retroviral drugs against AIDS exist. In attempts to develop such drugs, several stages of the HIV life cycle have been considered as targets for therapeutic intervention (Mitsuya, H. et al., 1991, FASEB J. 5:2369-2381). For example, virally encoded reverse transcriptase has been one focus of drug
30 development. A number of reverse-transcriptase-

targeted drugs, including 2',3'-dideoxynucleoside analogs such as AZT, ddI, ddC, and d4T have been developed which have been shown to be active against HIV (Mitsuya, H. et al., 1991, Science 249:1533-1544). While beneficial, these nucleoside analogs are not
5 curative, probably due to the rapid appearance of drug resistant HIV mutants (Lander, B. et al., 1989, Science 243:1731-1734). In addition, the drugs often exhibit toxic side effects such as bone marrow suppression, vomiting, and liver function
10 abnormalities.

Attempts are also being made to develop drugs which can inhibit viral entry into the cell, the earliest stage of HIV infection. Here, the focus has thus far been on CD4, the cell surface receptor for HIV. Recombinant soluble CD4; for example, has been
15 shown to inhibit infection of CD-4⁺ T-cells by some HIV-1 strains (Smith, D.H. et al., 1987, Science 238:1704-1707). Certain primary HIV-1 isolates, however, are relatively less sensitive to inhibition by recombinant CD-4 (Daar, E. et al., 1990, Proc.
20 Natl. Acad. Sci. USA 87:6574-6579). In addition, recombinant soluble CD-4 clinical trials have produced inconclusive results (Schooley, R. et al., 1990, Ann. Int. Med. 112:247-253; Kahn, J.O. et al., 1990, Ann. Int. Med. 112:254-261; Yarchoan, R. et al., 1989,
25 Proc. Vth Int. Conf. on AIDS, p. 564, MCP 137).

The late stages of HIV replication, which involve crucial virus-specific secondary processing of certain viral proteins, have also been suggested as possible anti-HIV drug targets. Late stage processing is
30 dependent on the activity of a viral protease, and drugs are being developed which inhibit this protease

(Erickson, J., 1990, Science 249:527-533). The clinical outcome of these candidate drugs is still in question.

Attention is also being given to the development of vaccines for the treatment of HIV infection. The
5 HIV-1 enveloped proteins (gp160, gp120, gp41) have been shown to be the major antigens for anti-HIV antibodies present in AIDS patients (Barin, et al., 1985, Science 228:1094-1096). Thus far, therefore, these proteins seem to be the most promising
10 candidates to act as antigens for anti-HIV vaccine development. To this end, several groups have begun to use various portions of gp160, gp120, and/or gp41 as immunogenic targets for the host immune system. See for example, Ivanoff, L. et al., U.S. Pat. No.
15 5,141,867; Saith, G. et al., WO 92/22,654; Shaffer, A., WO 91/09,872; Formoso, C. et al., WO 90/07,119. Clinical results concerning these candidate vaccines, however, still remain far in the future.

Thus, although a great deal of effort is being directed to the design and testing of anti-retroviral
20 drugs, a truly effective, non-toxic treatment is still needed.

3. SUMMARY OF THE INVENTION

25 The present invention relates, first, to DP178, a 36-amino acid synthetic peptide, also referred to herein as T20, corresponding to amino acids 638 to 673 of the transmembrane protein (TM) gp41 from the HIV-1 isolate LAI (HIV-1_{LAI}), which exhibits potent anti-
30 HIV-1 activity. The gp41 region from which DP178 is derived is referred to herein as HR2.

The invention further relates to those portions and analogs of DP178 which also show such antiviral activity, and/or show anti-membrane fusion capability, or an ability to modulate intracellular processes involving coiled-coil peptide structures. The term

5 "DP178 analog" refers to a peptide which contains an amino acid sequence corresponding to the DP178 peptide sequence present within the gp41 protein of HIV-1_{LAI}, but found in viruses and/or organisms other than HIV-1_{LAI}. Such DP178 analog peptides may, therefore,

10 correspond to DP178-like amino acid sequences present in other viruses, such as, for example, enveloped viruses, such as retroviruses other than HIV-1_{LAI}, as well as non-enveloped viruses. Further, such analogous DP178 peptides may also correspond to DP178-like amino acid sequences present in nonviral

15 organisms.

The invention further relates to DP107, a peptide, which is also referred to herein as T21, corresponding to amino acids 558-595 of the HIV-1_{LAI} transmembrane protein (TM) gp41. The gp41 region from

20 which DP107 is derived is referred to herein as HR1. The invention also relates to those portions and analogs of DP107 which that also show antiviral activity, and/or show anti-membrane fusion capability, or an ability to modulate intracellular processes

25 involving coiled-coil peptide structures. The term "DP107 analog" as used herein refers to a peptide which contains an amino acid sequence corresponding to the DP107 peptide sequence present within the gp41 protein of HIV-1_{LAI}, but found in viruses and organisms

30 other than HIV-1_{LAI}. Such DP107 analog peptides may, therefore, correspond to DP107-like amino acid

sequences present in other viruses, such as, for example, enveloped viruses, such as retroviruses other than HIV-1_{LAI}, as well as non-enveloped viruses. Further, such DP107 analog peptides may also correspond to DP107-like amino acid sequences present
5 in nonviral organisms.

Further, the peptides of the invention include DP107 analog and DP178 analog peptides having amino acid sequences recognized or identified by the 107x178x4, ALLMOTI5 and/or PLZIP search motifs
10 described herein.

The peptides of the invention may, for example, exhibit antifusogenic activity, antiviral activity, and/or may have the ability to modulate intracellular processes which involve coiled-coil peptide structures. With respect to the antiviral activity of
15 the peptides of the invention, such an antiviral activity includes, but is not limited to the inhibition of HIV transmission to uninfected CD-4⁺ cells. Additionally, the antifusogenic capability, antiviral activity or intracellular modulatory
20 activity of the peptides of the invention merely requires the presence of the peptides of the invention, and, specifically, does not require the stimulation of a host immune response directed against such peptides.

The peptides of the invention may be used, for example, as inhibitors of membrane fusion-associated events, such as, for example, the inhibition of human and non-human retroviral, especially HIV, transmission to uninfected cells. It is further contemplated that
30 the peptides of the invention may be used as

modulators of intracellular events involving coiled-coil peptide structures.

The peptides of the invention may, alternatively, be used to identify compounds, including small molecule compounds, which may themselves exhibit
5 antifusogenic, antiviral, or intracellular modulatory activity. For example, in one embodiment, the peptides of the invention are used to identify other DP178-like and/or DP107-like peptides that interact with each other and/or with their complementary HR1 or
10 HR2 domains with a lower affinity than the affinity exhibited by the "parent" or "native" DP178 or DP107 peptides from which they are derived. Such DP178-like and DP107-like peptides, which are also part of the present invention, may also be used, e.g., to identify
15 compounds, such as small molecule compounds, that exhibit antifusogenic, antiviral, or intracellular modulatory activity.

Additional uses include, for example, the use of the peptides of the invention as organism or viral type and/or subtype-specific diagnostic tools.

20 The terms "antifusogenic" and "anti-membrane fusion", as used herein, refer to an agent's ability to inhibit or reduce the level of membrane fusion events between two or more moieties relative to the level of membrane fusion which occurs between said
25 moieties in the absence of the peptide. The moieties may be, for example, cell membranes or viral structures, such as viral envelopes or pili. The term "antiviral", as used herein, refers to the compound's ability to inhibit viral infection of cells, via, for
30 example, cell-cell fusion or free virus infection. Such infection may involve membrane fusion, as occurs

in the case of enveloped viruses, or some other fusion event involving a viral structure and a cellular structure (e.g., such as the fusion of a viral pilus and bacterial membrane during bacterial conjugation).

It is also contemplated that the peptides of the invention may exhibit the ability to modulate intracellular events involving coiled-coil peptide structures. "Modulate", as used herein, refers to a stimulatory or inhibitory effect on the intracellular process of interest relative to the level or activity of such a process in the absence of a peptide of the invention.

Embodiments of the invention are demonstrated below wherein an extremely low concentration of DP178 (SEQ ID:1), and very low concentrations of a DP178 homolog (SEQ ID:3) are shown to be potent inhibitors of HIV-1 mediated CD-4⁺ cell-cell fusion (i.e., syncytial formation) and infection of CD-4⁺ cells by cell-free virus. Further, it is shown that DP178 (SEQ ID:1) is not toxic to cells, even at concentrations 3 logs higher than the inhibitory DP-178 (SEQ ID:1) concentration.

The present invention is based, in part, on the surprising discovery that the DP107 and DP178 domains of the HIV gp41 protein non-covalently complex with each other, and that their interaction is required for the normal infectivity of the virus. This discovery is described in the Example presented, below, in Section 8. The invention, therefore, further relates to methods for identifying antifusogenic, including antiviral, compounds that disrupt the interaction between DP107 and DP178, and/or between DP107-like and DP178-like peptides.

Additional embodiments of the invention (specifically, the Examples presents in Sections 9-16 and 19-25, below) are demonstrated, below, wherein peptides, from a variety of viral and nonviral sources, having structural and/or amino acid motif
5 similarity to DP107 and DP178 are identified, and search motifs for their identification are described. Further, Examples (in Sections 17, 18, 25-29) are presented wherein a number of the peptides of the invention are demonstrated exhibit substantial
10 antiviral activity or activity predictive of antiviral activity.

3.1. DEFINITIONS

Peptides are defined herein as organic compounds comprising two or more amino acids covalently joined
15 by peptide bonds. Peptides may be referred to with respect to the number of constituent amino acids, i.e., a dipeptide contains two amino acid residues, a tripeptide contains three, etc. Peptides containing ten or fewer amino acids may be referred to as
20 oligopeptides, while those with more than ten amino acid residues are polypeptides. Such peptides may also include any of the modifications and additional amino and carboxy groups as are described herein.

Peptide sequences defined herein are represented
25 by one-letter symbols for amino acid residues as follows:

A (alanine)
R (arginine)
N (asparagine)
D (aspartic acid)
C (cysteine)
30 Q (glutamine)
E (glutamic acid)

G (glycine)
H (histidine)
I (isoleucine)
L (leucine)
K (lysine)
M (methionine)
F (phenylalanine)
5 P (proline)
S (serine)
T (threonine)
W (tryptophan)
Y (tyrosine)
V (valine)

4. BRIEF DESCRIPTION OF THE FIGURES

10 FIG. 1. Amino acid sequence of DP178 (SEQ ID:1) derived from HIV_{LAI}; DP178 homologs derived from HIV-1_{SF2} (DP-185; SEQ ID:3), HIV-1_{RF} (SEQ ID:4), and HIV-1_{MN} (SEQ ID:5); DP178 homologs derived from amino acid sequences of two prototypic HIV-2 isolates, namely,
15 HIV-2_{rod} (SEQ ID:6) and HIV-2_{NIH2} (SEQ ID:7); control peptides: DP-180 (SEQ ID:2), a peptide incorporating the amino acid residues of DP178 in a scrambled sequence; DP-118 (SEQ ID:10) unrelated to DP178, which inhibits HIV-1 cell free virus infection; DP-125 (SEQ
20 ID:8), unrelated to DP178, also inhibits HIV-1 cell free virus infection; DP-116 (SEQ ID:9), unrelated to DP178, is negative for inhibition of HIV-1 infection when tested using a cell-free virus infection assay. Throughout the figures, the one letter amino acid code is used.

25 FIG. 2. Inhibition of HIV-1 cell-free virus infection by synthetic peptides. IC₅₀ refers to the concentration of peptide that inhibits RT production from infected cells by 50% compared to the untreated control. Control: the level of RT produced by

30

untreated cell cultures infected with the same level of virus as treated cultures.

FIG. 3. Inhibition of HIV-1 and HIV-2 cell-free virus infection by the synthetic peptide DP178 (SEQ ID:1). IC_{50} : concentration of peptide that inhibits
5 RT production by 50% compared to the untreated control. Control: Level of RT produced by untreated cell cultures infected with the same level of virus as treated cultures.

FIG. 4A-4B. Fusion Inhibition Assays. FIG 4A:
10 DP178 (SEQ ID:1) inhibition of HIV-1 prototypic isolate-mediated syncytial formation; data represents the number of virus-induced syncytial per cell. FIG. 4B: DP-180 (SEQ ID:2) represents a scrambled control peptide; DP-185 (SEQ ID:3) represents a DP178 homolog
15 derived from HIV-1_{SF2} isolate; Control, refers to the number of syncytial produced in the absence of peptide.

FIG. 5. Fusion inhibition assay: HIV-1 vs. HIV-2. Data represents the number of virus-induced syncytial per well. ND: not done.

20 FIG. 6. Cytotoxicity study of DP178 (SEQ ID:1) and DP-116 (SEQ ID:9) on CEM cells. Cell proliferation data is shown.

FIG. 7. Schematic representation of HIV-gp41 and maltose binding protein (MBP)-gp41 fusion
25 proteins. DP107 and DP178 are synthetic peptides based on the two putative helices of gp41. The letter P in the DP107 boxes denotes an Ile to Pro mutation at amino acid number 578. Amino acid residues are
numbered according to Meyers et al., "Human
30 Retroviruses and AIDS", 1991, Theoret. Biol. and Biophys. Group, Los Alamos Natl. Lab., Los Alamos, NM.

The proteins are more fully described, below, in Section 8.1.1.

FIG. 8. A point mutation alters the conformation and anti-HIV activity of M41.

FIG. 9. Abrogation of DP178 anti-HIV activity.

5 Cell fusion assays were carried out in the presence of 10 nM DP178 and various concentrations of M41Δ178 or M41PA178.

FIG. 10. Binding of DP178 to leucine zipper of gp41 analyzed by FAb-D ELISA.

10 FIG. 11A-B. Models for a structural transition in the HIV-1 TM protein. Two models are proposed which indicate a structural transition from a native oligomer to a fusogenic state following a trigger event (possibly gp120 binding to CD4). Common
15 features of both models include (1) the native state is held together by noncovalent protein-protein interactions to form the heterodimer of gp120/41 and other interactions, principally through gp41 interactive sites, to form homo-oligomers on the virus surface of the gp120/41 complexes; (2) shielding of
20 the hydrophobic fusogenic peptide at the N-terminus (F) in the native state; and (3) the leucine zipper domain (DP107) exists as a homo-oligomer coiled coil only in the fusogenic state. The major differences in the two models include the structural state (native or
25 fusogenic) in which the DP107 and DP178 domains are complexed to each other. In the first model (FIG. 11A) this interaction occurs in the native state and in the second (FIG. 11B), it occurs during the fusogenic state. When triggered, the fusion complex in the model depicted in (A) is generated through
30 formation of coiled-coil interactions in homologous

DP107 domains resulting in an extended α -helix. This conformational change positions the fusion peptide for interaction with the cell membrane. In the second model (FIG. 11B), the fusogenic complex is stabilized by the association of the DP178 domain with the DP107
5 coiled-coil.

FIG. 12. Motif design using heptad repeat positioning of amino acids of known coiled-coils.

FIG. 13. Motif design using proposed heptad repeat positioning of amino acids of DP107 and DP178.

10 FIG. 14. Hybrid motif design crossing GCN4 and DP107.

FIG. 15. Hybrid motif design crossing GCN4 and DP178.

15 FIG. 16. Hybrid motif design 107x178x4, crossing DP107 and DP178. This motif was found to be the most consistent at identifying relevant DP107-like and DP178-like peptide regions.

FIG. 17. Hybrid motif design crossing GCN4, DP107, and DP178.

20 FIG. 18. Hybrid motif design ALLMOTI5 crossing GCN4, DP107, DP178, c-Fos c-Jun, c-Myc, and Flu Loop 36.

FIG. 19. PLZIP motifs designed to identify N-terminal proline-leucine zipper motifs.

25 FIG. 20. Search results for HIV-1 (BRU isolate) enveloped protein gp41. Sequence search motif designations: Spades (♠): 107x178x4; Hearts (♥) ALLMOTI5; Clubs (♣): PLZIP; Diamonds (♦): transmembrane region (the putative transmembrane domains were identified using a PC/Gene program designed to search for such peptide regions).
30 Asterisk (*): Lupas method. The amino acid sequences

identified by each motif are bracketed by the respective characters. Representative sequences chosen based on 107x178x4 searches are underlined and in bold. DP107 and DP178 sequences are marked, and additionally double-underlined and italicized.

5 FIG. 21. Search results for human respiratory syncytial virus (RSV) strain A2 fusion glycoprotein F1. Sequence search motif designations are as in FIG. 20.

10 FIG. 22. Search results for simian immunodeficiency virus (SIV) enveloped protein gp41 (AGM3 isolate). Sequence search motif designations are as in FIG. 20.

15 FIG. 23. Search results for canine distemper virus (strain Onderstepoort) fusion glycoprotein 1. Sequence search motif designations are as in FIG. 20.

 FIG. 24. Search results for newcastle disease virus (strain Australia-Victoria/32) fusion glycoprotein F1. Sequence search motif designations are as in FIG. 20.

20 FIG. 25. Search results for human parainfluenza 3 virus (strain NIH 47885) fusion glycoprotein F1. Sequence search motif designations are as in FIG. 20.

25 FIG. 26. Search results for influenza A virus (strain A/AICHI/2/68) hemagglutinin precursor HA2. Sequence search designations are as in FIG. 20.

30 FIG. 27A-D. Respiratory Syncytial Virus (RSV) peptide antiviral and circular dichroism data. FIG. 27A-B: Peptides derived from the F2 DP178/DP107-like region. Antiviral and CD data. FIG. 27C-D:

Peptides derived from the F1 DP107-like region.
Peptide and CD data.

Antiviral activity (AV) is represented by the following qualitative symbols:

- "-", negative antiviral activity;
- 5 "+/-", antiviral activity at greater than 100 μ g/ml;
- "+", antiviral activity at between 50-100 μ g/ml;
- "++", antiviral activity at between 20-50 μ g/ml;
- "+++", antiviral activity at between 1-20 μ g/ml;
- 10 "++++", antiviral activity at <1 μ g/ml.

CD data, referring to the level of helicity is represented by the following qualitative symbol:

- "-", no helicity;
- "+", 25-50% helicity;
- 15 "++", 50-75% helicity;
- "+++", 75-100% helicity.

IC₅₀ refers to the concentration of peptide necessary to produce only 50% of the number of syncytial relative to infected control cultures containing no peptide. IC₅₀ values were obtained using
20 purified peptides only.

FIG. 28A-B. Respiratory Syncytial Virus (RSV) DP178-like region (F1) peptide antiviral and CD data. Antiviral symbols, CD symbols, and IC₅₀ are as in FIG. 27A-D. IC₅₀ values were obtained using
25 purified peptides only.

FIG. 29A-B. Peptides derived from the HPIV3 F1 DP107-like region. Peptide antiviral and CD data. Antiviral symbols, CD symbols, and IC₅₀ are as in FIG. 27A-D. Purified peptides were used to obtain IC₅₀ values, except where the values are marked by an
30

asterisk (*), in which cases, the IC_{50} values were obtained using a crude peptide preparation.

FIG. 29C. HPIV3 peptide T-184 CD spectrum at 1°C in 0.1M NaCl 10mM KPO_4 , pH 7.0. The data demonstrates the peptide's helical secondary structure
5 ($\theta_{222/208}=1.2$) over a wide range of concentrations (100-1500 μ M). This evidence is consistent with the peptide forming a helical coiled-coil structure.

FIG. 30A-B. Peptides derived from the HPIV3 F1 DP178-like region. Peptide antiviral and CD data.
10 Antiviral symbols, CD symbols, and IC_{50} are as in FIG. 27A-D. Purified peptides were used to obtain IC_{50} values, except where the values are marked by an asterisk (*), in which cases, the IC_{50} values were obtained using a crude peptide preparation.

FIG. 31. Motif search results for simian
15 immunodeficiency virus (SIV) isolate MM251, enveloped polyprotein gp41. Sequence search designations are as in FIG. 20.

FIG. 32. Motif search results for Epstein-Barr Virus (Strain B95-8), glycoprotein gp110
20 precursor (designated gp115). BALF4. Sequence search designations are as in FIG. 20.

FIG. 33. Motif search results for Epstein-Barr Virus (Strain B95-8), BZLF1 trans-activator protein (designated EB1 or Zebra). Sequence search
25 designations are as in FIG. 20. Additionally, "@" refers to a well known DNA binding domain and "+" refers to a well known dimerization domain, as defined by Flemington and Speck (Flemington, E. and Speck, S.H., 1990, Proc. Natl. Acad. Sci. USA 87:9459-9463).

FIG. 34. Motif search results for measles
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virus (strain Edmonston), fusion glycoprotein F1.

Sequence search designations are as in FIG. 20.

FIG. 35. Motif search results for Hepatitis B Virus (Subtype AYW), major surface antigen precursor S. Sequence search designations are as in FIG. 20.

5 FIG. 36. Motif search results for simian Mason-Pfizer monkey virus, enveloped (TM) protein gp20. Sequence search designations are as in FIG. 20.

FIG. 37. Motif search results for *Pseudomonas aeruginosa*, fimbrial protein (Pilin).
10 Sequence search designations are as in FIG. 20.

FIG. 38. Motif search results for *Neisseria gonorrhoeae* fimbrial protein (Pilin). Sequence search designations are as in FIG. 20.

FIG. 39. Motif search results for *Hemophilus influenzae* fimbrial protein. Sequence
15 search designations are as in FIG. 20.

FIG. 40. Motif search results for *Staphylococcus aureus*, toxic shock syndrome toxin-1. Sequence search designations are as in FIG. 20.

FIG. 41. Motif search results for
20 *Staphylococcus aureus* enterotoxin Type E. Sequence search designations are as in FIG. 20.

FIG. 42. Motif search results for *Staphylococcus aureus* enterotoxin A. Sequence search designations are as in FIG. 20.

25 FIG. 43. Motif search results for *Escherichia coli*, heat labile enterotoxin A. Sequence search designations are as in FIG. 20.

FIG. 44. Motif search results for human c-fos proto-oncoprotein. Sequence search designations
30 are as in FIG. 20.

FIG. 45. Motif search results for human lupus KU autoantigen protein P70. Sequence search designations are as in FIG. 20.

FIG. 46. Motif search results for human zinc finger protein 10. Sequence search designations
5 are as in FIG. 20.

FIG. 47. Measles virus (MeV) fusion protein DP178-like region antiviral and CD data. Antiviral symbols, CD symbols, and IC_{50} are as in FIG. 27A-D. IC_{50} values were obtained using purified peptides.

FIG. 48. Simian immunodeficiency virus (SIV) TM (fusion) protein DP178-like region antiviral data. Antiviral symbols are as in FIG. 27A-D "NT",
10 not tested.

FIG. 49A-C. DP178-derived peptide antiviral data. The peptides listed herein were derived from
15 the region surrounding the HIV-1 BRU isolate DP178 region (e.g., gp41 amino acid residues 615-717).

In instances where peptides contained DP178 point mutations, the mutated amino acid residues are shown with a shaded background. In instances in which the
20 test peptide has had an amino and/or carboxy-terminal group added or removed (apart from the standard amido- and acetyl- blocking groups found on such peptides), such modifications are indicated. FIG. 49A: The column to the immediate right of the name of the test
25 peptide indicates the size of the test peptide and points out whether the peptide is derived from a one amino acid peptide "walk" across the DP178 region. The next column to the right indicates whether the test peptide contains a point mutation, while the column to its right indicates whether certain amino
30 acid residues have been added to or removed from the

DP178-derived amino acid sequence. FIG 49B: The column to the immediate right of the test peptide name indicates whether the peptide represents a DP178 truncation, the next column to the right points out whether the peptide contains a point mutation, and the
5 column to its right indicates whether the peptide contains amino acids which have been added to or removed from the DP178 sequence itself. FIG. 49C: The column to the immediate right of the test peptide name indicates whether the test peptide contains a
10 point mutation, while the column to its right indicates whether amino acid residues have been added to or removed from the DP178 sequence itself. IC_{50} is as defined in FIG. 27A-D, and IC_{50} values were obtained using purified peptides except where marked with an
15 asterisk (*), in which case the IC_{50} was obtained using a crude peptide preparation.

FIG. 50. DP107 and DP107 gp41 region truncated peptide antiviral data. IC_{50} as defined in FIG. 27A-D, and IC_{50} values were obtained using purified peptides except where marked with an asterisk
20 (*), in which case the IC_{50} was obtained using a crude peptide preparation.

FIG. 51A-B. Epstein-Barr virus Strain B95-8 BZLF1 DP178/DP107 analog region peptide walks and electrophoretic mobility shift assay results. The
25 peptides (T-423 to T-446, FIG. 51A; T-447 to T-461, FIG. 51B) represent one amino acid residue "walks" through the EBV Zebra protein region from amino acid residue 173 to 246.

The amino acid residue within this region which corresponds to the first amino acid residue of each
30 peptide is listed to the left of each peptide, while

the amino acid residue within this region which corresponds to the last amino acid residue of each peptide is listed to the right of each peptide. The length of each test peptide is listed at the far right of each line, under the heading "Res".

5 "ACT" refers to a test peptide's ability to inhibit Zebra binding to its response element. "+" refers to a visible, but incomplete, abrogation of the response element/Zebra homodimer complex; "+++" refers to a complete abrogation of the complex; and "-"
10 represents a lack of complex disruption.

FIG. 52A-B. Hepatitis B virus subtype AYW major surface antigen precursor S protein DP178/DP107 analog region and peptide walks. 52A depicts Domain I (S protein amino acid residues 174-220), which contains a
15 peptides are listed which represent one amino acid peptide "walks" through domain I. 52B depicts Domain II (S protein amino acid residues 233-291), which contains a second potential DP178/DP107 analog region. In addition, peptides are listed which represent one
20 amino acid peptide "walks" through domain II.

FIG. 53: Cell fusion and competitive inhibition data for alanine walk experiments for the DP178-like Respiratory Syncytial Virus (RSV) peptide T112.

FIG. 54: Circular dichroism, cell fusion and
25 competitive inhibition data for alanine walk experiments for the peptide T20, which is also known as DP178.

5. DETAILED DESCRIPTION OF THE INVENTION

30 Described herein are peptides which may exhibit antifusogenic activity, antiviral capability, and/or

the ability to modulate intracellular processes involving coiled-coil peptide structures. The peptides described include, first, DP178 (SEQ ID NO:1), a gp41-derived 36 amino acid peptide and fragments and analogs of DP178.

5 In addition, the peptides of the invention described herein include peptides which are DP107 analogs. DP107 (SEQ ID NO:25) is a 38 amino acid peptide corresponding to residues 558 to 595 of the HIV-1_{LAI} transmembrane (TM) gp41 protein. Such DP107
10 analogs may exhibit antifusogenic capability, antiviral activity or an ability to modulate intracellular processes involving coiled-coil structures.

15 Further, peptides of the invention include DP107 and DP178 are described herein having amino acid sequences recognized by the 107x178x4, ALLMOTIS, and PLZIP search motifs. Such motifs are also discussed.

20 Also described here are antifusogenic, antiviral, intracellular modulatory, and diagnostic uses of the peptides of the invention. Further, procedures are described for the use of the peptides of the invention for the identification of compounds exhibiting antifusogenic, antiviral or intracellular modulatory activity.

25 While not limited to any theory of operation, the following model is proposed to explain the potent anti-HIV activity of DP178, based, in part, on the experiments described in the Examples, *infra*. In the HIV protein, gp41, DP178 corresponds to a putative α -helix region located in the C-terminal end of the gp41 ectodomain, and appears to associate with a distal
30 site on gp41 whose interactive structure is influenced

by the leucine zipper motif, a coiled-coil structure, referred to as DP107. The association of these two domains may reflect a molecular linkage or "molecular clasp" intimately involved in the fusion process. It is of interest that mutations in the C-terminal α -helix motif of gp41 (i.e., the D178 domain) tend to enhance the fusion ability of gp41, whereas mutations in the leucine zipper region (i.e., the DP107 domain) decrease or abolish the fusion ability of the viral protein. It may be that the leucine zipper motif is involved in membrane fusion while the C-terminal α -helix motif serves as a molecular safety to regulate the availability of the leucine zipper during virus-induced membrane fusion.

On the basis of the foregoing, two models are proposed of gp41-mediated membrane fusion which are schematically shown in FIG. 11A-B. The reason for proposing two models is that the temporal nature of the interaction between the regions defined by DP107 and DP178 cannot, as yet, be pinpointed. Each model envisions two conformations for gp41 - one in a "native" state as it might be found on a resting virion. The other in a "fusogenic" state to reflect conformational changes triggered following binding of gp120 to CD4 and just prior to fusion with the target cell membrane. The strong binding affinity between gp120 and CD4 may actually represent the trigger for the fusion process obviating the need for a pH change such as occurs for viruses that fuse within intracellular vesicles. The two major features of both models are: (1) the leucine zipper sequences (DP107) in each chain of oligomeric enveloped are held apart in the native state and are only allowed access

to one another in the fusogenic state so as to form the extremely stable coiled-coils, and (2) association of the DP178 and DP107 sites as they exist in gp41 occur either in the native or fusogenic state. FIG. 11A depicts DP178/DP107 interaction in the native
5 state as a molecular clasp. On the other hand, if one assumes that the most stable form of the enveloped occurs in the fusogenic state, the model in FIG. 11B can be considered.

When synthesized as peptides, both DP107 and
10 DP178 are potent inhibitors of HIV infection and fusion, probably by virtue of their ability to form complexes with viral gp41 and interfere with its fusogenic process; e.g., during the structural transition of the viral protein from the native
15 structure to the fusogenic state, the DP178 and DP107 peptides may gain access to their respective binding sites on the viral gp41, and exert a disruptive influence. DP107 peptides which demonstrate anti-HIV activity are described in Applicants' co-pending application Serial No. 08/264,531, filed June 23,
20 1994, which is incorporated by reference herein in its entirety.

As shown in the Examples, infra, a truncated recombinant gp41 protein corresponding to the ectodomain of gp41 containing both DP107 and DP178
25 domains (excluding the fusion peptide, transmembrane region and cytoplasmic domain of gp41) did not inhibit HIV-1 induced fusion. However, when a single mutation was introduced to disrupt the coiled-coil structure of the DP107 domain -- a mutation which results in a
30 total loss of biological activity of DP107 peptides -- the inactive recombinant protein was transformed to an

active inhibitor of HIV-1 induced fusion. This transformation may result from liberation of the potent DP178 domain from a molecular clasp with the leucine zipper, DP107 domain.

For clarity of discussion, the invention will be
5 described primarily for DP178 peptide inhibitors of HIV. However, the principles may be analogously applied to other viruses, both enveloped and nonenveloped, and to other non-viral organisms.

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5.1. DP178 AND DP178-LIKE PEPTIDES

The DP178 peptide (SEQ ID:1) of the invention corresponds to amino acid residues 638 to 673 of the transmembrane protein gp41 from the HIV-1_{LA1} isolate, and has the 36 amino acid sequence (reading from amino
5 to carboxy terminus):

NH₂-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-COOH (SEQ ID:1)

In addition to the full-length DP178 (SEQ ID:1)
10 36-mer, the peptides of the invention may include truncations of the DP178 (SEQ ID:1) peptide which exhibit antifusogenic activity, antiviral activity and/or the ability to modulate intracellular processes involving coiled-coil peptide structures. Truncations
15 of DP178 (SEQ ID:1) peptides may comprise peptides of between 3 and 36 amino acid residues (*i.e.*, peptides ranging in size from a tripeptide to a 36-mer polypeptide), as shown in Tables I and IA, below. Peptide sequences in these tables are listed from amino (left) to carboxy (right) terminus. "X" may
20 represent an amino group (-NH₂) and "Z" may represent a carboxyl (-COOH) group. Alternatively, "X" may represent a hydrophobic group, including but not limited to carbobenzyl, dansyl, or T-butoxycarbonyl; an acetyl group; a 9-fluorenylmethoxy-carbonyl (Fmoc)
25 group; or a covalently attached macromolecular group, including but not limited to a lipid-fatty acid conjugate, polyethylene glycol, carbohydrate or peptide group. Further, "Z" may represent an amido group; a T-butoxycarbonyl group; or a covalently
30 attached macromolecular group, including but not limited to a lipid-fatty acid conjugate, polyethylene

glycol, carbohydrate or peptide group. A preferred "X" or "Z" macromolecular group is a peptide group.

TABLE I
DP178 (SEQ ID:1) CARBOXY TRUNCATIONS

5	X-YTS-Z
	X-YTSL-Z
	X-YTSLI-Z
	X-YTSLIH-Z
	X-YTSLIHS-Z
	X-YTSLIHSL-Z
	X-YTSLIHSLI-Z
	X-YTSLIHSLIE-Z
10	X-YTSLIHSLIEE-Z
	X-YTSLIHSLIEES-Z
	X-YTSLIHSLIEESQ-Z
	X-YTSLIHSLIEESQN-Z
	X-YTSLIHSLIEESQNNQ-Z
	X-YTSLIHSLIEESQNNQQ-Z
	X-YTSLIHSLIEESQNNQQE-Z
	X-YTSLIHSLIEESQNNQQEK-Z
15	X-YTSLIHSLIEESQNNQQEKN-Z
	X-YTSLIHSLIEESQNNQQEKNE-Z
	X-YTSLIHSLIEESQNNQQEKNEQ-Z
	X-YTSLIHSLIEESQNNQQEKNEQE-Z
	X-YTSLIHSLIEESQNNQQEKNEQEL-Z
	X-YTSLIHSLIEESQNNQQEKNEQELL-Z
	X-YTSLIHSLIEESQNNQQEKNEQELLE-Z
20	X-YTSLIHSLIEESQNNQQEKNEQELLELD-Z
	X-YTSLIHSLIEESQNNQQEKNEQELLELDK-Z
	X-YTSLIHSLIEESQNNQQEKNEQELLELDKW-Z
	X-YTSLIHSLIEESQNNQQEKNEQELLELDKWA-Z
	X-YTSLIHSLIEESQNNQQEKNEQELLELDKWASL-Z
	X-YTSLIHSLIEESQNNQQEKNEQELLELDKWASLW-Z
	X-YTSLIHSLIEESQNNQQEKNEQELLELDKWASLWN-Z
25	X-YTSLIHSLIEESQNNQQEKNEQELLELDKWASLWNW-Z
	X-YTSLIHSLIEESQNNQQEKNEQELLELDKWASLWNWF-Z

The one letter amino acid code is used.

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TABLE IA
DP178 (SEQ ID:1) AMINO TRUNCATIONS

	X-NWF-Z
	X-WNWF-Z
	X-LWNWF-Z
	X-SLWNWF-Z
5	X-ASLWNWF-Z
	X-WASLWNWF-Z
	X-KWASLWNWF-Z
	X-DKWASLWNWF-Z
	X-LDKWASLWNWF-Z
	X-ELDKWASLWNWF-Z
	X-LELDKWASLWNWF-Z
	X-LLELDKWASLWNWF-Z
10	X-ELLELDKWASLWNWF-Z
	X-QELLELDKWASLWNWF-Z
	X-EQELLELDKWASLWNWF-Z
	X-NEQELLELDKWASLWNWF-Z
	X-KNEQELLELDKWASLWNWF-Z
	X-EKNEQELLELDKWASLWNWF-Z
	X-QEKNEQELLELDKWASLWNWF-Z
	X-QQEKNEQELLELDKWASLWNWF-Z
15	X-NQQEKNEQELLELDKWASLWNWF-Z
	X-QNQQEKNEQELLELDKWASLWNWF-Z
	X-SQNQQEKNEQELLELDKWASLWNWF-Z
	X-ESQNQQEKNEQELLELDKWASLWNWF-Z
	X-EESQNQQEKNEQELLELDKWASLWNWF-Z
	X-IEESQNQQEKNEQELLELDKWASLWNWF-Z
	X-LIEESQNQQEKNEQELLELDKWASLWNWF-Z
	X-SLIEESQNQQEKNEQELLELDKWASLWNWF-Z
20	X-HSLIEESQNQQEKNEQELLELDKWASLWNWF-Z
	X-IHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z
	X-LIHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z
	X-SLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z
	X-TSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z
	X-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z

The one letter amino acid code is used.

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The peptides of the invention also include DP178-like peptides. "DP178-like", as used herein, refers, first, to DP178 and DP178 truncations which contain one or more amino acid substitutions, insertions and/or deletions. Second, "DP-178-like" refers to
5 peptide sequences identified or recognized by the ALLMOTI5, 107x178x4 and PLZIP search motifs described herein, having structural and/or amino acid motif similarity to DP178. The DP178-like peptides of the invention may exhibit antifusogenic or antiviral
10 activity, or may exhibit the ability to modulate intracellular processes involving coiled-coil peptides. Further, such DP178-like peptides may possess additional advantageous features, such as, for example, increased bioavailability, and/or stability, or reduced host immune recognition.

15 HIV-1 and HIV-2 enveloped proteins are structurally distinct, but there exists a striking amino acid conservation within the DP178-corresponding regions of HIV-1 and HIV-2. The amino acid conservation is of a periodic nature, suggesting some
20 conservation of structure and/or function. Therefore, one possible class of amino acid substitutions would include those amino acid changes which are predicted to stabilize the structure of the DP178 peptides of the invention. Utilizing the DP178 and DP178 analog
25 sequences described herein, the skilled artisan can readily compile DP178 consensus sequences and ascertain from these, conserved amino acid residues which would represent preferred amino acid substitutions.

30 The amino acid substitutions may be of a conserved or non-conserved nature. Conserved amino acid substitutions consist of replacing one or more

amino acids of the DP178 (SEQ ID:1) peptide sequence with amino acids of similar charge, size, and/or hydrophobicity characteristics, such as, for example, a glutamic acid (E) to aspartic acid (D) amino acid substitution. Non-conserved substitutions consist of replacing one or more amino acids of the DP178 (SEQ ID:1) peptide sequence with amino acids possessing dissimilar charge, size, and/or hydrophobicity characteristics, such as, for example, a glutamic acid (E) to valine (V) substitution.

- 10 Amino acid insertions may consist of single amino acid residues or stretches of residues. The insertions may be made at the carboxy or amino terminal end of the DP178 or DP178 truncated peptides, as well as at a position internal to the peptide. Such insertions will generally range from 2 to 15 amino acids in length. It is contemplated that insertions made at either the carboxy or amino terminus of the peptide of interest may be of a broader size range, with about 2 to about 50 amino acids being preferred. One or more such insertions may be introduced into DP178 (SEQ.ID:1) or DP178 truncations, as long as such insertions result in peptides which may still be recognized by the 107x178x4, ALLMOT15 or PLZIP search motifs described herein, or may, alternatively, exhibit antifusogenic or antiviral activity, or exhibit the ability to modulate intracellular processes involving coiled-coil peptide structures.
- 25 Preferred amino or carboxy terminal insertions are peptides ranging from about 2 to about 50 amino acid residues in length, corresponding to gp41 protein regions either amino to or carboxy to the actual DP178 gp41 amino acid sequence, respectively. Thus, a
- 30

preferred amino terminal or carboxy terminal amino acid insertion would contain gp41 amino acid sequences found immediately amino to or carboxy to the DP178 region of the gp41 protein.

- Deletions of DP178 (SEQ ID:1) or DP178 truncations are also within the scope of the invention. Such deletions consist of the removal of one or more amino acids from the DP178 or DP178-like peptide sequence, with the lower limit length of the resulting peptide sequence being 4 to 6 amino acids.
- Such deletions may involve a single contiguous or greater than one discrete portion of the peptide sequences. One or more such deletions may be introduced into DP178 (SEQ.ID:1) or DP178 truncations, as long as such deletions result in peptides which may still be recognized by the 107x178x4, ALLMOTI5 or PLZIP search motifs described herein, or may, alternatively, exhibit antifusogenic or antiviral activity, or exhibit the ability to modulate intracellular processes involving coiled-coil peptide structures.
- DP178 analogs are further described, below, in Section 5.3.

5.2. DP107 AND DP107-LIKE PEPTIDES

- Further, the peptides of the invention include peptides having amino acid sequences corresponding to DP107 analogs. DP107 is a 38 amino acid peptide which exhibits potent antiviral activity, and corresponds to residues 558 to 595 of HIV-1_{LAI} transmembrane (TM) gp41 protein, as shown here:

- NH₂-NNLLRAIEAQQHLLQLTVWQIKQLQARILAVERYLKDQ-COOH
(SEQ ID:25)

In addition to the full-length DP107 (SEQ ID:25) 38-mer, the peptides of the invention may include truncations of the DP107 (SEQ ID:25) peptide which exhibit antifusogenic activity, antiviral activity and/or the ability to modulate intracellular processes involving coiled-coil peptide structures. Truncations of DP107 (SEQ ID:25) peptides may comprise peptides of between 3 and 38 amino acid residues (i.e., peptides ranging in size from a tripeptide to a 38-mer polypeptide), as shown in Tables II and IIA, below.

Peptide sequences in these tables are listed from amino (left) to carboxy (right) terminus. "X" may represent an amino group (-NH₂) and "Z" may represent a carboxyl (-COOH) group. Alternatively, "X" may represent a hydrophobic group, including but not limited to carbobenzyl, dansyl, or T-butoxycarbonyl; an acetyl group; a 9-fluorenylmethoxy-carbonyl (Fmoc) group; or a covalently attached macromolecular group, including but not limited to a lipid-fatty acid conjugate, polyethylene glycol, carbohydrate or peptide group. Further, "Z" may represent an amido group; a T-butoxycarbonyl group; or a covalently attached macromolecular group, including but not limited to a lipid-fatty acid conjugate, polyethylene glycol, carbohydrate or peptide group. A preferred "X" or "Z" macromolecular group is a peptide group.

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TABLE II
DP107 (SEQ ID:25) CARBOXY TRUNCATIONS

	X-NNL-Z
	X-NNLL-Z
	X-NNLLR-Z
5	X-NNLLRA-Z
	X-NNLLRAI-Z
	X-NNLLRAIE-Z
	X-NNLLRAIEA-Z
	X-NNLLRAIEAQ-Z
	X-NNLLRAIEAQQ-Z
	X-NNLLRAIEAQQH-Z
	X-NNLLRAIEAQQHL-Z
10	X-NNLLRAIEAQQHLL-Z
	X-NNLLRAIEAQQHLLQ-Z
	X-NNLLRAIEAQQHLLQL-Z
	X-NNLLRAIEAQQHLLQLT-Z
	X-NNLLRAIEAQQHLLQLTV-Z
	X-NNLLRAIEAQQHLLQLTVW-Z
	X-NNLLRAIEAQQHLLQLTVWQ-Z
	X-NNLLRAIEAQQHLLQLTVWQI-Z
15	X-NNLLRAIEAQQHLLQLTVWQIK-Z
	X-NNLLRAIEAQQHLLQLTVWQIKQ-Z
	X-NNLLRAIEAQQHLLQLTVWQIKQL-Z
	X-NNLLRAIEAQQHLLQLTVWQIKQLQ-Z
	X-NNLLRAIEAQQHLLQLTVWQIKQLQA-Z
	X-NNLLRAIEAQQHLLQLTVWQIKQLQAR-Z
	X-NNLLRAIEAQQHLLQLTVWQIKQLQARI-Z
	X-NNLLRAIEAQQHLLQLTVWQIKQLQARIL-Z
20	X-NNLLRAIEAQQHLLQLTVWQIKQLQARILA-Z
	X-NNLLRAIEAQQHLLQLTVWQIKQLQARILAV-Z
	X-NNLLRAIEAQQHLLQLTVWQIKQLQARILAVE-Z
	X-NNLLRAIEAQQHLLQLTVWQIKQLQARILAVER-Z
	X-NNLLRAIEAQQHLLQLTVWQIKQLQARILAVEY-Z
	X-NNLLRAIEAQQHLLQLTVWQIKQLQARILAVEYK-Z
	X-NNLLRAIEAQQHLLQLTVWQIKQLQARILAVEYKQ-Z
25	X-NNLLRAIEAQQHLLQLTVWQIKQLQARILAVEYKQD-Z

The one letter amino acid code is used.

TABLE IIA
DP178 (SEQ ID:25) AMINO TRUNCATIONS

	X-KDQ- Z
	X-LKDQ- Z
	X-YLKDQ- Z
5	X-RYLKDQ- Z
	X-ERYLKDQ- Z
	X-VERYLKDQ- Z
	X-AVERYLKDQ- Z
	X-LAVERYLKDQ- Z
	X-ILAVERYLKDQ- Z
	X-RILAVERYLKDQ- Z
10	X-ARILAVERYLKDQ- Z
	X-QARILAVERYLKDQ- Z
	X-LQARILAVERYLKDQ- Z
	X-QLQARILAVERYLKDQ- Z
	X-KQLQARILAVERYLKDQ- Z
	X-IKQLQARILAVERYLKDQ- Z
	X-QIKQLQARILAVERYLKDQ- Z
	X-WQIKQLQARILAVERYLKDQ- Z
	X-VWQIKQLQARILAVERYLKDQ- Z
15	X-TVWQIKQLQARILAVERYLKDQ- Z
	X-LTVWQIKQLQARILAVERYLKDQ- Z
	X-QLTVWQIKQLQARILAVERYLKDQ- Z
	X-LQLTVWQIKQLQARILAVERYLKDQ- Z
	X-LLQLTVWQIKQLQARILAVERYLKDQ- Z
	X-HLLQLTVWQIKQLQARILAVERYLKDQ- Z
	X-QHLLQLTVWQIKQLQARILAVERYLKDQ- Z
20	X-QQHLLQLTVWQIKQLQARILAVERYLKDQ- Z
	X-AQQHLLQLTVWQIKQLQARILAVERYLKDQ- Z
	X-EAQQHLLQLTVWQIKQLQARILAVERYLKDQ- Z
	X-IEAQQHLLQLTVWQIKQLQARILAVERYLKDQ- Z
	X-AIEAQQHLLQLTVWQIKQLQARILAVERYLKDQ- Z
	X-RAIEAQQHLLQLTVWQIKQLQARILAVERYLKDQ- Z
	X-LRAIEAQQHLLQLTVWQIKQLQARILAVERYLKDQ- Z
	X-LLRAIEAQQHLLQLTVWQIKQLQARILAVERYLKDQ- Z
	X-NLLRAIEAQQHLLQLTVWQIKQLQARILAVERYLKDQ- Z
25	X-NNLLRAIEAQQHLLQLTVWQIKQLQARILAVERYLKDQ- Z

The one letter amino acid code is used.

30

The peptides of the invention also include DP107-like peptides. "DP107-like", as used herein, refers, first, to DP107 and DP107 truncations which contain one or more amino acid substitutions, insertions and/or deletions. Second, "DP-107-like" refers to
5 peptide sequences identified or recognized by the ALLMOTI5, 107x178x4 and PLZIP search motifs described herein, having structural and/or amino acid motif similarity to DP107. The DP107-like peptides of the invention may exhibit antifusogenic or antiviral
10 activity, or may exhibit the ability to modulate intracellular processes involving coiled-coil peptides. Further, such DP107-like peptides may possess additional advantageous features, such as, for example, increased bioavailability, and/or stability, or reduced host immune recognition.

15 HIV-1 and HIV-2 enveloped proteins are structurally distinct, but there exists a striking amino acid conservation within the DP107-corresponding regions of HIV-1 and HIV-2. The amino acid conservation is of a periodic nature, suggesting some
20 conservation of structure and/or function. Therefore, one possible class of amino acid substitutions would include those amino acid changes which are predicted to stabilize the structure of the DP107 peptides of the invention. Utilizing the DP107 and DP107 analog
25 sequences described herein, the skilled artisan can readily compile DP107 consensus sequences and ascertain from these, conserved amino acid residues which would represent preferred amino acid substitutions.

30 The amino acid substitutions may be of a conserved or non-conserved nature. Conserved amino acid substitutions consist of replacing one or more

amino acids of the DP107 (SEQ ID:25) peptide sequence with amino acids of similar charge, size, and/or hydrophobicity characteristics, such as, for example, a glutamic acid (E) to aspartic acid (D) amino acid substitution. Non-conserved substitutions consist of
5 replacing one or more amino acids of the DP107 (SEQ ID:25) peptide sequence with amino acids possessing dissimilar charge, size, and/or hydrophobicity characteristics, such as, for example, a glutamic acid (E) to valine (V) substitution.

10 Amino acid insertions may consist of single amino acid residues or stretches of residues. The insertions may be made at the carboxy or amino terminal end of the DP107 or DP107 truncated peptides, as well as at a position internal to the peptide.
15 Such insertions will generally range from 2 to 15 amino acids in length. It is contemplated that insertions made at either the carboxy or amino terminus of the peptide of interest may be of a broader size range, with about 2 to about 50 amino acids being preferred. One or more such insertions
20 may be introduced into DP107 (SEQ.ID:25) or DP107 truncations, as long as such insertions result in peptides which may still be recognized by the 107x178x4, ALLMOTI5 or PLZIP search motifs described herein, or may, alternatively, exhibit antifusogenic
25 or antiviral activity, or exhibit the ability to modulate intracellular processes involving coiled-coil peptide structures.

Preferred amino or carboxy terminal insertions are peptides ranging from about 2 to about 50 amino acid residues in length, corresponding to gp41 protein
30 regions either amino to or carboxy to the actual DP107 gp41 amino acid sequence, respectively. Thus, a

preferred amino terminal or carboxy terminal amino acid insertion would contain gp41 amino acid sequences found immediately amino to or carboxy to the DP107 region of the gp41 protein.

Deletions of DP107 (SEQ ID:25) or DP178 truncations are also within the scope of the invention. Such deletions consist of the removal of one or more amino acids from the DP107 or DP107-like peptide sequence, with the lower limit length of the resulting peptide sequence being 4 to 6 amino acids. Such deletions may involve a single contiguous or greater than one discrete portion of the peptide sequences. One or more such deletions may be introduced into DP107 (SEQ.ID:25) or DP107 truncations, as long as such deletions result in peptides which may still be recognized by the 107x178x4, ALLMOTI5 or PLZIP search motifs described herein, or may, alternatively, exhibit antifusogenic or antiviral activity, or exhibit the ability to modulate intracellular processes involving coiled-coil peptide structures. DP107 and DP107 truncations are more fully described in Applicants' co-pending U.S. Patent Application Ser. No. 08/374,666, filed January 27, 1995, and which is incorporated herein by reference in its entirety. DP107 analogs are further described, below, in Section 5.3.

5.3. DP107 and DP178 ANALOGS

Peptides corresponding to analogs of the DP178, DP178 truncations, DP107 and DP107 truncation sequences of the invention, described, above, in Sections 5.1 and 5.2 may be found in other viruses,

including, for example, non-HIV-1_{LAI} enveloped viruses, non-enveloped viruses and other non-viral organisms.

The term "analog", as used herein, refers to a peptide which is recognized or identified via the 107x178x4, ALLMOTI5 and/or PLZIP search strategies
5 discussed below. Further, such peptides may exhibit antifusogenic capability, antiviral activity, or the ability to modulate intracellular processes involving coiled-coil structures.

Such DP178 and DP107 analogs may, for example,
10 correspond to peptide sequences present in TM proteins of enveloped viruses and may, additionally correspond to peptide sequences present in non enveloped and non-viral organisms. Such peptides may exhibit antifusogenic activity, antiviral activity, most
15 particularly antiviral activity which is specific to the virus in which their native sequences are found, or may exhibit an ability to modulate intracellular processes involving coiled-coil peptide structures.

DP178 analogs are peptides whose amino acid sequences are comprised of the amino acid sequences of
20 peptide regions of, for example, other (i.e., other than HIV-1_{LAI}) viruses that correspond to the gp41 peptide region from which DP178 (SEQ ID:1) was derived. Such viruses may include, but are not limited to, other HIV-1 isolates and HIV-2 isolates.
25 DP178 analogs derived from the corresponding gp41 peptide region of other (i.e., non HIV-1_{LAI}) HIV-1 isolates may include, for example, peptide sequences as shown below.

30 NH₂-YTNTIYTLLEESQNQQEKNEQELLELDKWASLWNWF-COOH
(DP-185; SEQ ID:3);

NH₂-YTGIIYNLLEESQNQQEKNEQELLELDKWANLWNWF-COOH (SEQ ID:4);

NH₂-YTSLIYSLLEKSQIQQEKNEQELLELDKWASLWNWF-COOH

(SEQ ID:5).

5 SEQ ID:3 (DP-185), SEQ ID:4, and SEQ ID:5 are derived from HIV-1_{SF2}, HIV-1_{RF}, and HIV-1_{MN} isolates, respectively. Underlined amino acid residues refer to those residues that differ from the corresponding position in the DP178 (SEQ ID:1) peptide. One such
10 DP178 analog, DP-185 (SEQ ID:3), is described in the Example presented in Section 6, below, where it is demonstrated that DP-185 (SEQ ID:3) exhibits antiviral activity. The DP178 analogs of the invention may also include truncations, as described above. Further, the
15 analogs of the invention modifications such those described for DP178 analogs in Section 5.1., above. It is preferred that the DP178 analogs of the invention represent peptides whose amino acid sequences correspond to the DP178 region of the gp41 protein, it is also contemplated that the peptides of
20 the invention may, additionally, include amino sequences, ranging from about 2 to about 50 amino acid residues in length, corresponding to gp41 protein regions either amino to or carboxy to the actual DP178 amino acid sequence.

25 Striking similarities, as shown in FIG. 1, exist within the regions of HIV-1 and HIV-2 isolates which correspond to the DP178 sequence. A DP178 analog derived from the HIV-2_{NIH2} isolate has the 36 amino acid sequence (reading from amino to carboxy terminus):

30 NH₂-LEANISQSLEQAQIQQEKMYELQKLNSWDVFTNWL-COOH (SEQ ID:7)

Table III and Table IV show some possible truncations of the HIV-2_{NIH2} DP178 analog, which may comprise peptides of between 3 and 36 amino acid residues (i.e., peptides ranging in size from a tripeptide to a 36-mer polypeptide). Peptide sequences in these

5 tables are listed from amino (left) to carboxy (right) terminus. "X" may represent an amino group (-NH₂) and "Z" may represent a carboxyl (-COOH) group. Alternatively, "X" may represent a hydrophobic group, including but not limited to carbobenzyl, dansyl, or

10 T-butoxycarbonyl; an acetyl group; a 9-fluorenylmethoxy-carbonyl (Fmoc) group; or a covalently attached macromolecular group, including but not limited to a lipid-fatty acid conjugate, polyethylene glycol, carbohydrate or peptide group.

15 Further, "Z" may represent an amido group; a T-butoxycarbonyl group; or a covalently attached macromolecular group, including but not limited to a lipid-fatty acid conjugate, polyethylene glycol, carbohydrate or peptide group. A preferred "X" or "Z"

20 macromolecular group is a peptide group.

20

25

30

TABLE IIIHIV-2_{NIH2} DP178 analog carboxy truncations.

	X-LEA-Z
	X-LEAN-Z
	X-LEANI-Z
	X-LEANIS-Z
5	X-LEANISQ-Z
	X-LEANISQS-Z
	X-LEANISQSL-Z
	X-LEANISQSLE-Z
	X-LEANISQSLEQ-Z
	X-LEANISQSLEQA-Z
	X-LEANISQSLEQAQ-Z
	X-LEANISQSLEQAQI-Z
10	X-LEANISQSLEQAQIQ-Z
	X-LEANISQSLEQAQIQQ-Z
	X-LEANISQSLEQAQIQQE-Z
	X-LEANISQSLEQAQIQQEK-Z
	X-LEANISQSLEQAQIQQEK-N-Z
	X-LEANISQSLEQAQIQQEK-NM-Z
	X-LEANISQSLEQAQIQQEK-NMY-Z
	X-LEANISQSLEQAQIQQEK-NMYE-Z
15	X-LEANISQSLEQAQIQQEK-NMYEL-Z
	X-LEANISQSLEQAQIQQEK-NMYELQ-Z
	X-LEANISQSLEQAQIQQEK-NMYELQK-Z
	X-LEANISQSLEQAQIQQEK-NMYELQKL-Z
	X-LEANISQSLEQAQIQQEK-NMYELQKLN-Z
	X-LEANISQSLEQAQIQQEK-NMYELQKLNS-Z
	X-LEANISQSLEQAQIQQEK-NMYELQKLNSW-Z
	X-LEANISQSLEQAQIQQEK-NMYELQKLNSWD-Z
20	X-LEANISQSLEQAQIQQEK-NMYELQKLNSWDV-Z
	X-LEANISQSLEQAQIQQEK-NMYELQKLNSWDVF-Z
	X-LEANISQSLEQAQIQQEK-NMYELQKLNSWDVFT-Z
	X-LEANISQSLEQAQIQQEK-NMYELQKLNSWDVFTN-Z
	X-LEANISQSLEQAQIQQEK-NMYELQKLNSWDVFTNW-Z
	X-LEANISQSLEQAQIQQEK-NMYELQKLNSWDVFTNWL-Z

The one letter amino acid code is used.

25

30

TABLE IV
HIV-2_{NIH2} DP178 analog amino truncations.

	X-NWL-Z
	X-TNWL-Z
	X-FTNWL-Z
	X-VFTNWL-Z
	X-DVFTNWL-Z
5	X-WDVFTNWL-Z
	X-SWDVFTNWL-Z
	X-NSWDVFTNWL-Z
	X-LNSWDVFTNWL-Z
	X-KLNSWDVFTNWL-Z
	X-QKLNSWDVFTNWL-Z
	X-LQKLNSWDVFTNWL-Z
	X-ELQKLNSWDVFTNWL-Z
10	X-YELQKLNSWDVFTNWL-Z
	X-MYELQKLNSWDVFTNWL-Z
	X-NMYELQKLNSWDVFTNWL-Z
	X-KNMYELQKLNSWDVFTNWL-Z
	X-EKNMYELQKLNSWDVFTNWL-Z
	X-QEKNMYELQKLNSWDVFTNWL-Z
	X-QQEKNMYELQKLNSWDVFTNWL-Z
	X-IQQEKNMYELQKLNSWDVFTNWL-Z
15	X-QIQQEKNMYELQKLNSWDVFTNWL-Z
	X-AQIQQEKNMYELQKLNSWDVFTNWL-Z
	X-QAQIQQEKNMYELQKLNSWDVFTNWL-Z
	X-EAQIQQEKNMYELQKLNSWDVFTNWL-Z
	X-LEAQIQQEKNMYELQKLNSWDVFTNWL-Z
	X-SLEAQIQQEKNMYELQKLNSWDVFTNWL-Z
	X-QSLEAQIQQEKNMYELQKLNSWDVFTNWL-Z
	X-SQSLEAQIQQEKNMYELQKLNSWDVFTNWL-Z
20	X-ISQSLEAQIQQEKNMYELQKLNSWDVFTNWL-Z
	X-NISQSLEAQIQQEKNMYELQKLNSWDVFTNWL-Z
	X-ANISQSLEAQIQQEKNMYELQKLNSWDVFTNWL-Z
	X-EANISQSLEAQIQQEKNMYELQKLNSWDVFTNWL-Z
	X-LEANISQSLEAQIQQEKNMYELQKLNSWDVFTNWL-Z

The one letter amino acid code is used.

25

30

DP178 and DP107 analogs are recognized or identified, for example, by utilizing one or more of the 107x178x4, ALLMOTI5 or PLZIP computer-assisted search strategies described and demonstrated, below, in the Examples presented in Sections 9 through 16 and 19 through 25. The search strategy identifies additional peptide regions which are predicted to have structural and/or amino acid sequence features similar to those of DP107 and/or DP178.

The search strategies are described fully, below, in the Example presented in Section 9. While this search strategy is based, in part, on a primary amino acid motif deduced from DP107 and DP178, it is not based solely on searching for primary amino acid sequence homologies, as such protein sequence homologies exist within, but not between major groups of viruses. For example, primary amino acid sequence homology is high within the TM protein of different strains of HIV-1 or within the TM protein of different isolates of simian immunodeficiency virus (SIV). Primary amino acid sequence homology between HIV-1 and SIV, however, is low enough so as not to be useful. It is not possible, therefore, to find peptide regions similar to DP107 or DP178 within other viruses, or within non-viral organisms, whether structurally, or otherwise, based on primary sequence homology, alone.

Further, while it would be potentially useful to identify primary sequence arrangements of amino acids based on, for example, the physical chemical characteristics of different classes of amino acids rather than based on the specific amino acids themselves, such search strategies have, until now, proven inadequate. For example, a computer algorithm designed by Lupas et al. to identify coiled-coil

propensities of regions within proteins (Lupas, A., et al., 1991 Science 252:1162-1164) is inadequate for identifying protein regions analogous to DP107 or DP178.

Specifically, analysis of HIV-1 gp160 (containing
5 both gp120 and gp41) using the Lupas algorithm does not identify the coiled-coil region within DP107. It does, however, identify a region within DP178 beginning eight amino acids N-terminal to the start of DP178 and ending eight amino acids from the C-
10 terminus. The DP107 peptide has been shown experimentally to form a stable coiled coil. A search based on the Lupas search algorithm, therefore, would not have identified the DP107 coiled-coil region. Conversely, the Lupas algorithm identified the DP178
15 region as a potential coiled-coil motif. However, the peptide derived from the DP178 region failed to form a coiled coil in solution.

A possible explanation for the inability of the Lupas search algorithm to accurately identify coiled-coil sequences within the HIV-1 TM, is that the Lupas
20 algorithm is based on the structure of coiled coils from proteins that are not structurally or functionally similar to the TM proteins of viruses, antiviral peptides (e.g. DP107 and DP178) of which are an object of this invention.

25 The computer search strategy of the invention, as demonstrated in the Examples presented below, in Sections 9 through 16 and 19 through 25, successfully identifies regions of proteins similar to DP107 or DP178. This search strategy was designed to be used
30 with a commercially-available sequence database package, preferably PC/Gene.

A series of search motifs, the 107x178x4, ALLMOTI5 and PLZIP motifs, were designed and engineered to range in stringency from strict to broad, as discussed in this Section and in Section 9, with 107x178x4 being preferred. The sequences
5 identified via such search motifs, such as those listed in Tables V-XIV, below, potentially exhibit antifusogenic, such as antiviral, activity, may additionally be useful in the identification of antifusogenic, such as antiviral, compounds, and are
10 intended to be within the scope of the invention.

Coiled-coiled sequences are thought to consist of heptad amino acid repeats. For ease of description, the amino acid positions within the heptad repeats are sometimes referred to as A through G, with the first
15 position being A, the second B, etc. The motifs used to identify DP107-like and DP178-like sequences herein are designed to specifically search for and identify such heptad repeats. In the descriptions of each of the motifs described, below, amino acids enclosed by
20 brackets , i.e., [], designate the only amino acid residues that are acceptable at the given position, while amino acids enclosed by braces, i.e., {}, designate the only amino acids which are unacceptable at the given heptad position. When a set of bracketed or braced amino acids is followed by a number in
25 parentheses i.e., (), it refers to the number of subsequent amino acid positions for which the designated set of amino acids hold, e.g, a (2) means "for the next two heptad amino acid positions".

30

The ALLMOTI5 is written as follows:

```
{CDGHP} - {CFP} (2) - {CDGHP} - {CFP} (3) -
{CDGHP} - {CFP} (2) - {CDGHP} - {CFP} (3) -
{CDGHP} - {CFP} (2) - {CDGHP} - {CFP} (3) -
{CDGHP} - {CFP} (2) - {CDGHP} - {CFP} (3) -
{CDGHP} - {CFP} (2) - {CDGHP} - {CFP} (3) -
```

5 Translating this motif, it would read: "at the first (A) position of the heptad, any amino acid residue except C, D, G, H, or P is acceptable, at the next two (B,C) amino acid positions, any amino acid residue except C, F, or P is acceptable, at the fourth
10 heptad position (D), any amino acid residue except C, D, G, H, or P is acceptable, at the next three (E, F, G) amino acid positions, any amino acid residue except C, F, or P is acceptable. This motif is designed to search for five consecutive heptad repeats (thus the repeat of the first line five times), meaning that it
15 searches for 35-mer sized peptides. It may also be designed to search for 28-mers, by only repeating the initial motif four times. With respect to the ALLMOTI5 motif, a 35-mer search is preferred. Those viral (non-bacteriophage) sequences identified via
20 such an ALLMOTI5 motif are listed in Table V in U.S. Patent Application No. 08/470,896 filed on June 6, 1995 which is incorporated herein by reference in its entirety. These viral sequences potentially exhibit antiviral activity, may be useful in the the
25 identification of antiviral compounds, and are intended to be within the scope of the invention. In those instances wherein a single gene exhibits greater than one sequence recognized by the ALLMOTI5 search motif, the amino acid residue numbers of these sequences are listed under "Area 2", "Area 3", etc.
30 This convention is used for each of the Tables listed, below, at the end of this Section.

The 107x178x4 motif is written as follows:

[EFIKLNQSTVWY] - {CFMP} (2) - [EFIKLNQSTVWY] - {CFMP} (3) -
 [EFIKLNQSTVWY] - {CFMP} (2) - [EFIKLNQSTVWY] - {CFMP} (3) -
 [EFIKLNQSTVWY] - {CFMP} (2) - [EFIKLNQSTVWY] - {CFMP} (3) -
 [EFIKLNQSTVWY] - {CFMP} (2) - [EFIKLNQSTVWY] - {CFMP} (3) -

Translating this motif, it would read: "at the
 5 first (A) position of the heptad, only amino acid
 residue E, F, I, K, L, N, Q, S, T, V, W, or Y is
 acceptable, at the next two (B,C) amino acid
 positions, any amino acid residue except C, F, M or P
 is acceptable, at the fourth position (D), only amino
 10 acid residue E, F, I, K, L, N, Q, S, T, V, W, or Y is
 acceptable, at the next three (E, F, G) amino acid
 positions, any amino acid residue except C, F, M or P
 is acceptable. This motif is designed to search for
 four consecutive heptad repeats (thus the repeat of
 15 the first line four times), meaning that it searches
 for 28-mer sized peptides. It may also be designed to
 search for 35-mers, by repeating the initial motif
 five times. With respect to the 107x178x4 motif, a
 28-mer search is preferred.

Those viral (non-bacteriophage) sequences
 20 identified via such a 107x178x4 motif are listed in
 Table VI in U.S. Patent Application No. 08/470,896
 filed on June 6, 1995, which is incorporated herein,
 by reference, in its entirety. Those viral (non-
 bacteriophage) sequences listed in Table VII of U.S.
 25 Patent Application No. 08/470,896 (incorporated herein
 by reference in its entirety) are particularly
 preferred.

The 107x178x4 search motif was also utilized to
 identify non-viral procaryotic protein sequences, as
 listed in Table VIII in U.S. Patent Application No.
 30 08/470,896 filed on June 6, 1995, which is
 incorporated herein, by reference, in its entirety.

Further, this search motif was used to reveal a number of human proteins. The results of this human protein 107x178x4 search is listed in Table IX in U.S. Patent Application No. 08/470,896 filed on June 6, 1995, which is incorporated herein, by reference, in its entirety. The sequences listed in Tables VIII and IX, therefore, reveal peptides which may be useful as antifusogenic compounds or in the identification of antifusogenic compounds, and are intended to be within the scope of the invention.

10 The PLZIP series of motifs are as listed in FIG. 19. These motifs are designed to identify leucine zipper coiled-coil like heptads wherein at least one proline residue is present at some predefined distance N-terminal to the repeat. These PLZIP motifs find regions of proteins with similarities to HIV-1 DP178
15 generally located just N-terminal to the transmembrane anchor. These motifs may be translated according to the same convention described above. Each line depicted in FIG. 19 represents a single, complete search motif. "X" in these motifs refers to any amino
20 acid residue. In instances wherein a motif contains two numbers within parentheses, this refers to a variable number of amino acid residues. For example, X (1,12) is translated to "the next one to twelve amino acid residues, inclusive, may be any amino
25 acid".

 Tables X through XIV in U.S. Patent Application No. 08/470,896 filed on June 6, 1995 (which is incorporated herein, by reference, in its entirety), list sequences identified via searches conducted with such PLZIP motifs. Specifically, Table X lists viral
30 sequences identified via PCTLZIP, P1CTLZIP and P2CTLZIP search motifs, Table XI lists viral sequences

identified via P3CTLZIP, P4CTLZIP, P5CTLZIP and
P6CTLZIP search motifs, Table XII lists viral sequences
identified via P7CTLZIP, P8CTLZIP and P9CTLZIP search
motifs, Table XIII lists viral sequences identified
via P12LZIPC searches and Table XIV lists viral
5 sequences identified via P23TLZIPC search motifs. The
viral sequences listed in these tables represent
peptides which potentially exhibit antiviral activity,
may be useful in the identification of antiviral
compounds, and are intended to be within the scope of
10 the invention.

The Examples presented in Sections 17, 18, 26 and
27 below, demonstrate that viral sequences identified
via the motif searches described herein identify
substantial antiviral characteristics. Specifically,
15 the Example presented in Section 17 describes peptides
with anti-respiratory syncytial virus activity, the
Example presented in Section 18 describes peptides
with anti-parainfluenza virus activity, the Example
presented in Section 26 describes peptides with anti-
measles virus activity and the Example presented in
20 Section 27 describes peptides with anti-simian
immunodeficiency virus activity.

The DP107 and DP178 analogs may, further, contain
any of the additional groups described for DP178,
above, in Section 5.1. For example, these peptides
25 may include any of the additional amino-terminal
groups as described above for "X" groups, and may also
include any of the carboxy-terminal groups as
described, above, for "Z" groups.

Additionally, truncations of the identified DP107
and DP178 peptides are among the peptides of the
30 invention. Further, such DP107 and DP178 analogs and
DP107/DP178 analog truncations may exhibit one or more

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amino acid substitutions, insertion, and/or deletions. The DP178 analog amino acid substitutions, insertions and deletions, are as described, above, for DP178-like peptides in Section 5.1. The DP-107 analog amino acid substitutions, insertions and deletions are also as described, above, for DP107-like peptides in Section 5.2. Representative examples of such DP107/DP178 truncations are provided in Tables XV through XXII of U.S. Patent Application Serial No. 08/470,896 filed on June 6, 1995, which is incorporated herein by reference in its entirety.

10 Other exemplary DP178 and DP107 peptides and DP178-like and DP107-like peptides which are considered part of the present invention include the peptides described in U.S. Patent Application Serial No. 09/315,304 filed on May 4, 1999 which is incorporated by reference in its entirety. Such DP178 and DP107 peptides and DP178-like and DP107-like peptides include, e.g., the peptides listed below in Table V.

20 peptides include peptides described, e.g., in U.S. Patent Application Serial No. 08/038,387 filed on March 29, 1993, now U.S. Patent No. 5,627,023; in U.S. Patent Application Serial No. 08/073,028 filed on June 7, 1993, now U.S. Patent No. 5,464,933; in U.S. Patent Application Serial No. 08/255,208 filed on June, 7, 1994; in U.S. Patent Application Serial No. 08/360,107 filed on December 20, 1994 and in U.S. Patent Application Serial No. 08/470,896 filed on June 6, 1995 each of which is incorporated herein by reference in its entirety.

TABLE V

T No.	Sequence
1	GIKQLQARILAVERYLKDQ
2	NNLLRAIEAQQHLLQLTVW
3	NEQELLELDKQASLWNWF
4	YTSLIHSLIEESQNQOEK
5	Ac-VWGIKQLQARILAVERYLKDQQLLGIWG-NH2
6	QHLLQLTVWGIKQLQARILAVERYLKDQ
7	LRAIEAQQHLLQLTVWGIKQLQARILAV
8	VQQQNLLRAIEAQQHLLQLTVWGIKQL
9	RQLLSGIVQQQNLLRAIEAQQHLLQLT
10	MTLTVQARQLLSGIVQQQNLLRAIEAQ
12	VVSLSNGVSVLTSKVLDLKNYIDKQLL
13	LLSTNKAVVSLSNGVSVLTSKVLDLKNY
15	Ac-VLHLEGEVNKIKSALLSTNKAVVSLSNG-NH2
19	Ac-LLSTNKAVVSLSNGVSVLTSKVLDLKNY-NH2
20	Ac-YTSLIHSLIEESQNQOEKNEQELLELDKQASLWNWF-NH2
21	Ac-NNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
22	Ac-IELSNIKENKCGTDAKVLIKQELDKYKNAVTELQLLMQST-NH2
23	Ac-IELSNIKENKCGTDAKVLIKQELDKY-NH2
24	Ac-ENKCGTDAKVLIKQELDKYKNAVTEL-NH2
25	Ac-DAKVLIKQELDKYKNAVTELQLLMQST-NH2
26	Ac-CNGTDAKVLIKQELDKYKNAVTELQLL-NH2
27	Ac-SNIKENKCGTDAKVLIKQELDKYKNAVTELQLL-NH2
28	Ac-ASGVAVSKVLHLEGEVNKIKSALLSTNKAVVSLSNGV-NH2
29	Ac-SGVAVSKVLHLEGEVNKIKSALLSTNKAVVSLSNG-NH2
30	Ac-VLHLEGEVNKIKSALLSTHKAVVSLSNGVSVLTSK-NH2
31	Ac-ARKLQRMKQLEDKVEELLSKNYHYLENEVARLKKLV-NH2
32	Ac-RMKQLEDKVEELLSKNYHYLENEVARLKKLVGER-NH2
33	Ac-VQQQNLLRAIEAQQHLLQLTVWGIKQL-NH2
34	Ac-LRAIEAQQHLLQLTVWGIKQLQARILAV-NH2
35	Ac-QHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
36	Ac-RQLLSGIVQQQNLLRAIEAQQHLLQLT-NH2
37	Ac-MTLTVQARQLLSGIVQQQNLLRAIEAQ-NH2
38	Ac-AKQARSDIEKLKEAIRDITNKAVQSVQSS-NH2
39	Ac-AAVALVEAKQARSDIEKLKEAIRDITNKAVQSVQSS-NH2
40	Ac-AKQARSDIEKLKEAIRDITNKAVQSVQSSIGNLIVA-NH2
41	Ac-GTIALGVATSAQITAVALVEAKQARSD-NH2
42	Ac-ATSAQITAVALVEAKQARSDIEKLKEA-NH2
43	Ac-AAVALVEAKQARSDIEKLKEAIRDITNKANH2
44	Ac-IEKLKEAIRDITNKAVQSVQSSIGNLIVA-NH2
45	Ac-IRDITNKAVQSVQSSIGNLIVAIAKSVQDY-NH2
46	Ac-AVQSVQSSIGNLIVAIAKSVQDYVNKEIV-NH2
47	Ac-QARQLLSGIVQQQNLLRAIEAQQHLLQLTVWGIKQLARILAVERYLKDQ-NH2
48	Ac-QARQLLSGIVQQQNLLRAIEAQQHLLQ-NH2
49	Ac-MTWEMDREINNYTSLIGSLIEESQNQOEKNEQELLELDKQASLWNWF-NH2
50	Ac-WMEWDREINNYTSLIGSLIEESQNQOEKNEQELLE-NH2
51	Ac-INNYTSLIGSLIEESQNQOEKNEQELLE-NH2
52	Ac-INNYTSLIGSLIEESQNQOEKNEQELLELDKQASL-NH2
53	Ac-EWDREINNYTSLIGSLIEESQNQOEKNEQEGGC-NH2
54	Ac-QSRTLLAGIVQQQQLLDVVKRQOELLR-NH2

T	No.	Sequence
	55	Ac-NNDTWQEWERKVDFFLEENITALLEEAAQIQQEKKNMYELQKLSWD-NH2
	56	Ac-WQEWERKVDFFLEENITALLEEAAQIQQEK-NH2
	57	Ac-VDFLEENITALLEEAAQIQQEKKNMYELQK-NH2
	58	Ac-ITALLEEAAQIQQEKKNMYELQKLSWDVF-NH2
	59	Ac-SSESFTLLEQWNNWKLQAEQWLEQINEKHYLEDIS-NH2
5	60	Ac-DKASLWNNWF-NH2
	61	Ac-NEQELLELDKASLWNNWF-NH2
	62	Ac-EKNEQELLELDKASLWNNWF-NH2
	63	Ac-NQQEKNEQELLELDKASLWNNWF-NH2
	64	Ac-ESQNQQEKNEQELLELDKASLWNNWF-NH2
	65	Ac-LIHSLEESQNQQEKNEQELLELDKASLWNNWF-NH2
	66	Ac-NDQKKLMSNNVQIVRQSYSIMSIIEE-NH2
	67	Ac-DEFDASISQVNEKINQSLAFIRKSDELL-NH2
	68	Ac-VSKGYSALRTGWYTSVITIELSNIKEN-NH2
10	69	Ac-VVSLSNGVSVLTSKVLDLKNYIDKQLL-NH2
	70	Ac-VNKIKSALLSTNKAVVSLSNGVSVLTSK-NH2
	71	Ac-PIINFYDPLVFPSEFDASISQVNEKINQSLAFIR-NH2
	72	Ac-NLVYAQLQFTYDITLRYINRALAQIAEA-NH2
	73	Ac-LNQVDLTETLERYQQLNTYALVSKDASYRS-NH2
	74	Ac-ELLVLKKAQLNRHSYKDSDFLDAALD-NH2
	75	Ac-LAEAGEESVTEDTEREDTEEREDEEE-NH2
	76	Ac-ALLAEAGEESVTEDTEREDTEEREDEEEENEART-NH2
15	77	Ac-ETERSVDLVAALLAEAGEESVTEDTEREDTEERE-NH2
	78	Ac-EESVTEDTEREDTEEREDEEEENEART-NH2
	79	Ac-VDLVAALLAEAGEESVTEDTEREDTEEE-NH2
	80	Ac-NSETERSVDLVAALLAEAGEESVTE-NH2
	81	Ac-DISYAQLQFTYDVLKDYINDALRNIMDA-NH2
	82	Ac-SNVFSKDEIMREYNSQKHIRTLSAKVNDN-NH2
	83	Biotin-YTSLIHSLEESQNQQEKNEQELLELDKASLWNNWF-NH2
	84	Dig-YTSLIHSLEESQNQQEKNEQELLELDKASLWNNWF-NH2
20	85	Biotin-NNLLRAIEAQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
	86	Dig-NNLLRAIEAQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
	87	Ac-VLHQLNIQLKQYLETQERLLAGNRILARQLQIWKDVA-NH2
	88	Ac-LWHEQLLNTAQRAGLQLQLINQALAVREKVLIRYDIQK-NH2
	89	Ac-LLDNFESTWEQSKELWEQOEISIQNLHKSALQEW-NH2
	90	Ac-LSNLLQISNNSDEWLEALEIEHEKWKLTQWQSYEQF-NH2
	91	Ac-KLEALEGKLEALEGKLEALEGKLEALEGKLEALEGK-NH2
	92	Ac-ELRALRGELRALRGELRALRGELRALRGK-NH2
25	93	Ac-ELKAKELEGEGLAEAGEEALKGELLEKAAKLEGLELLK-NH2
	94	Ac-WEAAAREAAAREAAAREAAARA-NH2
	95	Ac-YTSLIHSLEESQNQQEKNEQELLELDKASLWNAF-NH2
	96	Ac-YTSLIHSLEESQNQQEKNEQELLELDKASLANWF-NH2
	97	Ac-YTSLIHSLEESQNQQEKKNQELLELDKASLWNNWF-NH2
	98	Ac-YTSLIHSLEESQNQQEKNEQELLQDKASLWNNWF-NH2
	99	Ac-YTSLIHSLEESQNQQEKKNQELLQDKASLWNNWF-NH2
	100	Ac-RMKQLEDKVEELLSKNYHLENEVARLKKLVGER-NH2
	101	Ac-QQLLQLTVWGIKQLQARILAVERYLKNQ-NH2
30	102	Ac-NEQELLELDKASLWNNWF-NH2
	103	Ac-YTSLIQSLIEESQNQQEKNEQELLELDKASLWNNWF-NH2
	104	Ac-IINFYDPLVFPSEFDASISQVNEKINQSLAFIRK-NH2

T	No.	Sequence
	105	Ac-INFYDPLVFPSPDEFDASISQVNEKINQSLAFIRKS-NH2
	106	Ac-NFYDPLVFPSPDEFDASISQVNEKINQSLAFIRKSD-NH2
	107	Ac-FYDPLVFPSPDEFDASISQVNEKINQSLAFIRKSDE-NH2
	108	Ac-YDPLVFPSPDEFDASISQVNEKINQSLAFIRKSDEL-NH2
	109	Ac-DPLVFPSPDEFDASISQVNEKINQSLAFIRKSDELL-NH2
5	110	Ac-PLVFPSPDEFDASISQVNEKINQSLAFIRKSDELLH-NH2
	111	Ac-LVFPSPDEFDASISQVNEKINQSLAFIRKSDELLHN-NH2
	112	Ac-VFPSPDEFDASISQVNEKINQSLAFIRKSDELLHNV-NH2
	113	Ac-FPSPDEFDASISQVNEKINQSLAFIRKSDELLHNVN-NH2
	114	Ac-PSDEFDASISQVNEKINQSLAFIRKSDELLHNVNA-NH2
	115	Ac-SDEFDASISQVNEKINQSLAFIRKSDELLHNVNAG-NH2
	116	Ac-DEFDASISQVNEKINQSLAFIRKSDELLHNVNAGK-NH2
	117	Ac-EFDASISQVNEKINQSLAFIRKSDELLHNVNAGKS-NH2
	118	Ac-FDASISQVNEKINQSLAFIRKSDELLHNVNAGKST-NH2
10	119	Ac-DASISQVNEKINQSLAFIRKSDELLHNVNAGKSTT-NH2
	120	Ac-ASGVAVSKVLHLEGEVNKIKSALLSTNKAVVSLSN-NH2
	121	Ac-SGVAVSKVLHLEGEVNKIKSALLSTNKAVVSLSNG-NH2
	122	Ac-GVAVSKVLHLEGEVNKIKSALLSTNKAVVSLSNGV-NH2
	123	Ac-VAVSKVLHLEGEVNKIKSALLSTNKAVVSLSNGVS-NH2
	124	Ac-AVSKVLHLEGEVNKIKSALLSTNKAVVSLSNGVSV-NH2
	125	Ac-VSKVLHLEGEVNKIKSALLSTNKAVVSLSNGVSVL-NH2
	126	Ac-SKVLHLEGEVNKIKSALLSTNKAVVSLSNGVSVLT-NH2
15	127	Ac-KVLHLEGEVNKIKSALLSTNKAVVSLSNGVSVLTS-NH2
	128	Ac-VLHLEGEVNKIKSALLSTNKAVVSLSNGVSVLTSK-NH2
	129	Ac-LHLEGEVNKIKSALLSTNKAVVSLSNGVSVLTSKV-NH2
	130	Ac-HLEGEVNKIKSALLSTNKAVVSLSNGVSVLTSKVLD-NH2
	131	Ac-LEGEVNKIKSALLSTNKAVVSLSNGVSVLTSKVLDL-NH2
	132	Ac-EGEVNKKIKSALLSTNKAVVSLSNGVSVLTSKVLDL-NH2
	133	Ac-GEVNKKIKSALLSTNKAVVSLSNGVSVLTSKVLDLK-NH2
	134	Ac-EVNKKIKSALLSTNKAVVSLSNGVSVLTSKVLDLKN-NH2
20	135	Ac-VNKKIKSALLSTNKAVVSLSNGVSVLTSKVLDLKNY-NH2
	136	Ac-NKKIKSALLSTNKAVVSLSNGVSVLTSKVLDLKNYI-NH2
	137	Ac-KIKSALLSTNKAVVSLSNGVSVLTSKVLDLKNYID-NH2
	138	Ac-IKSALLSTNKAVVSLSNGVSVLTSKVLDLKNYIDK-NH2
	139	Ac-KSALLSTNKAVVSLSNGVSVLTSKVLDLKNYIDKQ-NH2
	140	Ac-SALLSTNKAVVSLSNGVSVLTSKVLDLKNYIDKQL-NH2
	141	Ac-ALLSTNKAVVSLSNGVSVLTSKVLDLKNYIDKQLL-NH2
	142	Ac-YTSVITIELSNIKENKCNGTDAKVLIKQELDKYK-NH2
25	143	Ac-TSVITIELSNIKENKCNGTDAKVLIKQELDKYKN-NH2
	144	Ac-SVITIELSNIKENKCNGTDAKVLIKQELDKYKNA-NH2
	145	Ac-VITIELSNIKENKCNGTDAKVLIKQELDKYKNAV-NH2
	146	Ac-ITIELSNIKENKCNGTDAKVLIKQELDKYKNAVTE-NH2
	147	Ac-TIELSNIKENKCNGTDAKVLIKQELDKYKNAVTEL-NH2
	148	Ac-IELSNIKENKCNGTDAKVLIKQELDKYKNAVTELO-NH2
	149	Ac-ELSNIKENKCNGTDAKVLIKQELDKYKNAVTELOL-NH2
	150	Ac-LSNIKENKCNGTDAKVLIKQELDKYKNAVTELOQL-NH2
30	151	Ac-SNIKENKCNGTDAKVLIKQELDKYKNAVTELOQLL-NH2
	152	Ac-NIKENKCNGTDAKVLIKQELDKYKNAVTELOQLLM-NH2
	153	Ac-IKENKCNGTDAKVLIKQELDKYKNAVTELOQLLMQ-NH2
	154	Ac-KENKCNGTDAKVLIKQELDKYKNAVTELOQLLMQS-NH2

T	No.	Sequence
	155	Ac-ENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST-NH2
	156	Ac-LLDNFESTWEQSKELWELQEISIQNLHKSALQEYWN-NH2
	157	Ac-ALGVATSAQITA AVALVEAKQARSDIEKLKEAIRD-NH2
	158	Ac-LGVATSAQITA AVALVEAKQARSDIEKLKEAIRD-T-NH2
	159	Ac-GVATSAQITA AVALVEAKQARSDIEKLKEAIRD-TN-NH2
5	160	Ac-VATSAQITA AVALVEAKQARSDIEKLKEAIRD-TNK-NH2
	161	Ac-ATSAQITA AVALVEAKQARSDIEKLKEAIRD-TNKA-NH2
	162	Ac-TSAQITA AVALVEAKQARSDIEKLKEAIRD-TNKAV-NH2
	163	Ac-SAQITA AVALVEAKQARSDIEKLKEAIRD-TNKAVQ-NH2
	164	Ac-AQITA AVALVEAKQARSDIEKLKEAIRD-TNKAVQS-NH2
	165	Ac-QITA AVALVEAKQARSDIEKLKEAIRD-TNKAVQSV-NH2
	166	Ac-ITA AVALVEAKQARSDIEKLKEAIRD-TNKAVQSVQ-NH2
	167	Ac-TA AVALVEAKQARSDIEKLKEAIRD-TNKAVQSVQS-NH2
	168	Ac-AAVALVEAKQARSDIEKLKEAIRD-TNKAVQSVQSS-NH2
10	169	Ac-AVALVEAKQARSDIEKLKEAIRD-TNKAVQSVQSSI-NH2
	170	Ac-VALVEAKQARSDIEKLKEAIRD-TNKAVQSVQSSIG-NH2
	171	Ac-ALVEAKQARSDIEKLKEAIRD-TNKAVQSVQSSIGN-NH2
	172	Ac-LVEAKQARSDIEKLKEAIRD-TNKAVQSVQSSIGNL-NH2
	173	Ac-VEAKQARSDIEKLKEAIRD-TNKAVQSVQSSIGNLI-NH2
	174	Ac-EAKQARSDIEKLKEAIRD-TNKAVQSVQSSIGNLIV-NH2
	175	Ac-KQARSDIEKLKEAIRD-TNKAVQSVQSSIGNLIVAI-NH2
	176	Ac-QARSDIEKLKEAIRD-TNKAVQSVQSSIGNLIVAIK-NH2
15	177	Ac-ARSDIEKLKEAIRD-TNKAVQSVQSSIGNLIVAIKS-NH2
	178	Ac-RSDIEKLKEAIRD-TNKAVQSVQSSIGNLIVAIKSV-NH2
	179	Ac-SDIEKLKEAIRD-TNKAVQSVQSSIGNLIVAIKSVQ-NH2
	180	Ac-DIEKLKEAIRD-TNKAVQSVQSSIGNLIVAIKSVQD-NH2
	181	Ac-IEKLKEAIRD-TNKAVQSVQSSIGNLIVAIKSVQDY-NH2
	182	Ac-EKLKEAIRD-TNKAVQSVQSSIGNLIVAIKSVQDYV-NH2
	183	Ac-KLKEAIRD-TNKAVQSVQSSIGNLIVAIKSVQDYVN-NH2
	184	Ac-LKEAIRD-TNKAVQSVQSSIGNLIVAIKSVQDYVNK-NH2
20	185	Ac-KEAIRD-TNKAVQSVQSSIGNLIVAIKSVQDYVNKE-NH2
	186	Ac-EAIRD-TNKAVQSVQSSIGNLIVAIKSVQDYVNKEI-NH2
	187	Ac-AIRD-TNKAVQSVQSSIGNLIVAIKSVQDYVNKEIV-NH2
	188	Ac-IRD-TNKAVQSVQSSIGNLIVAIKSVQDYVNKEIV-NH2
	189	Ac-YTPNDITLNNVALDPIDISIELNKA KSDLEESKE-NH2
	190	Ac-TPNDITLNNVALDPIDISIELNKA KSDLEESKEW-NH2
	191	Ac-PNDITLNNVALDPIDISIELNKA KSDLEESKEWI-NH2
	192	Ac-NDITLNNVALDPIDISIELNKA KSDLEESKEWIR-NH2
25	193	Ac-DITLNNVALDPIDISIELNKA KSDLEESKEWIRR-NH2
	194	Ac-ITLNNVALDPIDISIELNKA KSDLEESKEWIRRS-NH2
	195	Ac-TLNNVALDPIDISIELNKA KSDLEESKEWIRRSN-NH2
	196	Ac-LNNVALDPIDISIELNKA KSDLEESKEWIRRSNQ-NH2
	197	Ac-NNSVALDPIDISIELNKA KSDLEESKEWIRRSNQK-NH2
	198	Ac-NSVALDPIDISIELNKA KSDLEESKEWIRRSNQKL-NH2
	200	Ac-SVALDPIDISIELNKA KSDLEESKEWIRRSNQKLD-NH2
	201	Ac-VALDPIDISIELNKA KSDLEESKEWIRRSNQKLD-S-NH2
	202	Ac-ALDPIDISIELNKA KSDLEESKEWIRRSNQKLD-SI-NH2
30	203	Ac-LDPIDISIELNKA KSDLEESKEWIRRSNQKLD-SIG-NH2
	204	Ac-DPIDISIELNKA KSDLEESKEWIRRSNQKLD-SIGN-NH2
	205	Ac-PIDISIELNKA KSDLEESKEWIRRSNQKLD-SIGNW-NH2

T	No.	Sequence
	206	Ac-IDISIELNKAQSDLEESKEWIRRSNQKLD SIGNWH-NH2
	207	Ac-DISIELNKAQSDLEESKEWIRRSNQKLD SIGNWHQ-NH2
	208	Ac-ISIELNKAQSDLEESKEWIRRSNQKLD SIGNWHQS-NH2
	209	Ac-SIELNKAQSDLEESKEWIRRSNQKLD SIGNWHQSS-NH2
	210	Ac-IELNKAQSDLEESKEWIRRSNQKLD SIGNWHQSST-NH2
5	211	Ac-ELNKAQSDLEESKEWIRRSNQKLD SIGNWHQSSTT-NH2
	212	Ac-ELRALRGELRALRGELRALRGELRALRGELRALRGK-NH2
	213	Ac-YTSLIHSLIEESQNQQQKNEQEELLELDKWASLWNWF-NH2
	214	Ac-YTSLIHSLIEESQNQQEKNEQEELLELDKWASLWNWF-NH2
	215	Ac-YTSLIHSLIEESQNQQEKNEQEELLELDKWASLWNWF-NH2
	216	Ac-YTSLIHSLIEESQNQQEKNEQEELLELDKWASLWNWF-NH2
	217	Ac-YTSLIHSLIEESQNQQEKNEQEELLELDKWASLWNWF-NH2
	218	Ac-EQEELLELDKWASLWNWF-NH2
	219	Ac-QEELLELDKWASLWNWF-NH2
10	220	Ac-ELLELDKWASLWNWF-NH2
	221	Ac-LELDKWASLWNWF-NH2
	222	Ac-ELDKWASLWNWF-NH2
	226	Ac-WASLWNWF-NH2
	227	Ac-ASLWNWF-NH2
	229	Ac-YTSLIHSLIEESQNQQEKNEQEELLELDKWASLANAA-NH2
	230	Ac-YTSLIHSLIEESQNQQEKNEQEELLELDKWASLWNWF-NH2
	231	Ac-YTSLIQSLIEESQNQQEKNEQEELLELDKWASLWNWF-NH2
15	234	Ac-EAAAREAAAREAAARLELDKWASLWNWF-NH2
	236	Ac-PSLRDPISAEISIQALSALGGDINKVLEKLGYSG-NH2
	237	Ac-SLRDPISAEISIQALSALGGDINKVLEKLGYSGG-NH2
	238	Ac-LRDPISAEISIQALSALGGDINKVLEKLGYSGG-NH2
	239	Ac-RDPISAEISIQALSALGGDINKVLEKLGYSGGDL-NH2
	240	Ac-DPISAEISIQALSALGGDINKVLEKLGYSGGDLL-NH2
	241	Ac-PISAEISIQALSALGGDINKVLEKLGYSGGDLLG-NH2
	242	Ac-ISAESIQALSALGGDINKVLEKLGYSGGDLLGI-NH2
20	243	Ac-SAESIQALSALGGDINKVLEKLGYSGGDLLGIL-NH2
	244	Ac-AESIQALSALGGDINKVLEKLGYSGGDLLGILE-NH2
	245	Ac-EISIQALSALGGDINKVLEKLGYSGGDLLGILES-NH2
	246	Ac-ISIQALSALGGDINKVLEKLGYSGGDLLGILES-NH2
	247	Ac-SIQALSALGGDINKVLEKLGYSGGDLLGILES-NH2
	248	Ac-IQALSALGGDINKVLEKLGYSGGDLLGILES-NH2
	249	Ac-QALSALGGDINKVLEKLGYSGGDLLGILES-NH2
	250	Ac-ALSALGGDINKVLEKLGYSGGDLLGILES-NH2
25	251	Ac-LSALGGDINKVLEKLGYSGGDLLGILES-NH2
	252	Ac-PDAVYLHRIDLGPPISLERLDVGTNLGNAIAKLED-NH2
	253	Ac-DAVYLHRIDLGPPISLERLDVGTNLGNAIAKLEDA-NH2
	254	Ac-AVYLHRIDLGPPISLERLDVGTNLGNAIAKLEDAK-NH2
	255	Ac-VYLHRIDLGPPISLERLDVGTNLGNAIAKLEDAKE-NH2
	256	Ac-YLHRIDLGPPISLERLDVGTNLGNAIAKLEDAKEL-NH2
	257	Ac-LHRIDLGPPISLERLDVGTNLGNAIAKLEDAKELL-NH2
	258	Ac-HRIDLGPPISLERLDVGTNLGNAIAKLEDAKELLE-NH2
	259	Ac-RIDLGPPISLERLDVGTNLGNAIAKLEDAKELLESS-NH2
30	260	Ac-IDLGPPISLERLDVGTNLGNAIAKLEDAKELLESS-NH2
	261	Ac-DLGPPISLERLDVGTNLGNAIAKLEDAKELLESSD-NH2
	262	Ac-LGPPISLERLDVGTNLGNAIAKLEDAKELLESSDQ-NH2

T	No.	Sequence
	263	Ac-GPPISLERLDVGTNLGNIAIAKLEDAKELLESSDQI-NH2
	264	Ac-PPISLERLDVGTNLGNIAIAKLEDAKELLESSDQIL-NH2
	265	Ac-PISLERLDVGTNLGNIAIAKLEDAKELLESSDQILR-NH2
	266	Ac-ISLERLDVGTNLGNIAIAKLEDAKELLESSDQIRS-NH2
	267	Ac-SLERLDVGTNLGNIAIAKLEDAKELLESSDQILRSM-NH2
5	268	Ac-LERLDVGTNLGNIAIAKLEDAKELLESSDQILRSMK-NH2
	269	Ac-EWIRRSNQKLD SI-NH2
	270	Ac-LELDKWASLANAF-NH2
	271	Ac-LELDKWASLFNFF-NH2
	272	Ac-LELDKWASLANWF-NH2
	273	Ac-LELDKWASLWNAF-NH2
	274	Ac-ELGNVNNSISNALDKLEESNSKLDKVNKLTSTSA-NH2
	275	Ac-TELGNVNNSISNALDKLEESNSKLDKVNKLTSTS-NH2
	276	Ac-STELGNVNNSISNALDKLEESNSKLDKVNKLTST-NH2
10	277	Ac-ISTELGNVNNSISNALDKLEESNSKLDKVNKLTST-NH2
	278	Ac-DISTELGNVNNSISNALDKLEESNSKLDKVNKLT-NH2
	279	Ac-LDISTELGNVNNSISNALDKLEESNSKLDKVNKLT-NH2
	280	Ac-NLDISTELGNVNNSISNALDKLEESNSKLDKVNK-NH2
	281	Ac-GNLDISTELGNVNNSISNALDKLEESNSKLDKVN-NH2
	282	Ac-TGNLDISTELGNVNNSISNALDKLEESNSKLDKVN-NH2
	283	Ac-VTGNLDISTELGNVNNSISNALDKLEESNSKLDKV-NH2
	284	Ac-IVTGNLDISTELGNVNNSISNALDKLEESNSKLDK-NH2
15	285	Ac-VIVTGNLDISTELGNVNNSISNALDKLEESNSKLD-NH2
	286	Ac-QVIVTGNLDISTELGNVNNSISNALDKLEESNSKL-NH2
	287	Ac-SQVIVTGNLDISTELGNVNNSISNALDKLEESNSK-NH2
	288	Ac-DSQVIVTGNLDISTELGNVNNSISNALDKLEESNS-NH2
	289	Ac-LDSQVIVTGNLDISTELGNVNNSISNALDKLEESN-NH2
	290	Ac-ILDSQVIVTGNLDISTELGNVNNSISNALDKLEES-NH2
	291	Ac-SILDSQVIVTGNLDISTELGNVNNSISNALDKLEE-NH2
	292	Ac-ISILDSQVIVTGNLDISTELGNVNNSISNALDKLE-NH2
20	293	Ac-NISILDSQVIVTGNLDISTELGNVNNSISNALDKL-NH2
	294	Ac-KNISILDSQVIVTGNLDISTELGNVNNSISNALDK-NH2
	295	Ac-QKNISILDSQVIVTGNLDISTELGNVNNSISNALD-NH2
	296	Ac-YQKNISILDSQVIVTGNLDISTELGNVNNSISNAL-NH2
	297	Ac-TYQKNISILDSQVIVTGNLDISTELGNVNNSISNA-NH2
	298	Ac-ATYQKNISILDSQVIVTGNLDISTELGNVNNSISN-NH2
	299	Ac-DATYQKNISILDSQVIVTGNLDISTELGNVNNSIS-NH2
	300	Ac-FDATYQKNISILDSQVIVTGNLDISTELGNVNNSI-NH2
25	301	Ac-EFDTYQKNISILDSQVIVTGNLDISTELGNVNNS-NH2
	302	Ac-GEFDTYQKNISILDSQVIVTGNLDISTELGNVN-NH2
	303	Ac-SGEFDTYQKNISILDSQVIVTGNLDISTELGNVN-NH2
	304	Ac-LSGEFDTYQKNISILDSQVIVTGNLDISTELGNV-NH2
	305	Ac-RLSGEFDTYQKNISILDSQVIVTGNLDISTELGN-NH2
	306	Ac-LRLSGEFDTYQKNISILDSQVIVTGNLDISTELG-NH2
	307	Ac-TLRLSGEFDTYQKNISILDSQVIVTGNLDISTEL-NH2
	308	Ac-ITLRLSGEFDTYQKNISILDSQVIVTGNLDISTE-NH2
	309	Ac-GITLRLSGEFDTYQKNISILDSQVIVTGNLDIST-NH2
30	310	Ac-TATIEAVHEVTDGLSQLAVAVGKMQQFVNDQFNNT-NH2
	311	Ac-ITATIEAVHEVTDGLSQLAVAVGKMQQFVNDQFNN-NH2
	312	Ac-SITATIEAVHEVTDGLSQLAVAVGKMQQFVNDQFN-NH2

T	No.	Sequence
	314	Ac-KESITATIEAVHEVTDGLSQLAVAVGKMQQFVNDQ-NH2
	315	Ac-LKESITATIEAVHEVTDGLSQLAVAVGKMQQFVND-NH2
	316	Ac-RLKESITATIEAVHEVTDGLSQLAVAVGKMQQFVN-NH2
	317	Ac-LRLKESITATIEAVHEVTDGLSQLAVAVGKMQQFV-NH2
	318	Ac-ILRLKESITATIEAVHEVTDGLSQLAVAVGKMQQF-NH2
5	319	Ac-NILRLKESITATIEAVHEVTDGLSQLAVAVGKMQQ-NH2
	320	Ac-ANILRLKESITATIEAVHEVTDGLSQLAVAVGKMQ-NH2
	321	Ac-AANILRLKESITATIEAVHEVTDGLSQLAVAVGKM-NH2
	322	Ac-HKCDDECMNSVKNGTYDYPKYEEESKLNREIKGV-NH2
	323	Ac-KCDDECMNSVKNGTYDYPKYEEESKLNREIKGVK-NH2
	324	Ac-CDDECMNSVKNGTYDYPKYEEESKLNREIKGVKL-NH2
	325	Ac-DDECMNSVKNGTYDYPKYEEESKLNREIKGVKLS-NH2
	326	Ac-DECMNSVKNGTYDYPKYEEESKLNREIKGVKLSS-NH2
	327	Ac-ECMNSVKNGTYDYPKYEEESKLNREIKGVKLSSM-NH2
10	328	Ac-CMNSVKNGTYDYPKYEEESKLNREIKGVKLSSMG-NH2
	329	Ac-MNSVKNGTYDYPKYEEESKLNREIKGVKLSSMGV-NH2
	330	Ac-NSVKNGTYDYPKYEEESKLNREIKGVKLSSMGVY-NH2
	331	Ac-SVKNGTYDYPKYEEESKLNREIKGVKLSSMGVYQ-NH2
	332	Ac-VKNGTYDYPKYEEESKLNREIKGVKLSSMGVYQI-NH2
	333	Ac-KNGTYDYPKYEEESKLNREIKGVKLSSMGVYQIL-NH2
	334	Ac-AFIRKSDELLHN-NH2
	335	Ac-VVLAGAALGVATAAQITAGIALHQSMNSQAIDNL-NH2
15	336	Ac-VLAGAALGVATAAQITAGIALHQSMNSQAIDNLR-NH2
	337	Ac-LAGAALGVATAAQITAGIALHQSMNSQAIDNLRA-NH2
	338	Ac-AGAALGVATAAQITAGIALHQSMNSQAIDNLRAS-NH2
	339	Ac-GAALGVATAAQITAGIALHQSMNSQAIDNLRASL-NH2
	340	Ac-AALGVATAAQITAGIALHQSMNSQAIDNLRASLE-NH2
	341	Ac-ALGVATAAQITAGIALHQSMNSQAIDNLRASLET-NH2
	342	Ac-LGVATAAQITAGIALHQSMNSQAIDNLRASLETT-NH2
	343	Ac-GVATAAQITAGIALHQSMNSQAIDNLRASLETTN-NH2
20	344	Ac-VATAAQITAGIALHQSMNSQAIDNLRASLETTNQ-NH2
	345	Ac-ATAAQITAGIALHQSMNSQAIDNLRASLETTNQA-NH2
	346	Ac-TAAQITAGIALHQSMNSQAIDNLRASLETTNQAI-NH2
	347	Ac-AAQITAGIALHQSMNSQAIDNLRASLETTNQAIENH2
	348	Ac-AQITAGIALHQSMNSQAIDNLRASLETTNQAIENH2
	349	Ac-QITAGIALHQSMNSQAIDNLRASLETTNQAIENH2
	350	Ac-ITAGIALHQSMNSQAIDNLRASLETTNQAIENH2
	351	Ac-TAGIALHQSMNSQAIDNLRASLETTNQAIENH2
25	352	Ac-AGIALHQSMNSQAIDNLRASLETTNQAIENH2
	353	Ac-GIALHQSMNSQAIDNLRASLETTNQAIENH2
	354	Ac-IALHQSMNSQAIDNLRASLETTNQAIENH2
	355	Ac-ALHQSMNSQAIDNLRASLETTNQAIENH2
	356	Ac-LHQSMNSQAIDNLRASLETTNQAIENH2
	357	Ac-HQSMNSQAIDNLRASLETTNQAIENH2
	358	Ac-QSMLNSQAIDNLRASLETTNQAIENH2
	359	Ac-SMLNSQAIDNLRASLETTNQAIENH2
	360	Ac-MLNSQAIDNLRASLETTNQAIENH2
30	361	Ac-LSQAIDNLRASLETTNQAIENH2
	362	Ac-NSQAIDNLRASLETTNQAIENH2
	363	Ac-SQAIDNLRASLETTNQAIENH2

T No.	Sequence
364	Ac-QAIDNLRASLETTNQAIEAIRQAGQEMILAVQGVQ-NH2
365	Ac-AIDNLRASLETTNQAIEAIRQAGQEMILAVQGVQD-NH2
366	Ac-IDNLRASLETTNQAIEAIRQAGQEMILAVQGVQDY-NH2
367	Ac-DNLRASLETTNQAIEAIRQAGQEMILAVQGVQDYI-NH2
368	Ac-NLRASLETTNQAIEAIRQAGQEMILAVQGVQDYIN-NH2
369	Ac-LRASLETTNQAIEAIRQAGQEMILAVQGVQDYINN-NH2
5 370	Ac-RASLETTNQAIEAIRQAGQEMILAVQGVQDYINNE-NH2
371	Ac-YTSVITIELSNIKENKUNGTDVAVKLIKQELDKYK-NH2
372	Ac-TSVITIELSNIKENKUNGTDVAVKLIKQELDKYKN-NH2
373	Ac-SVITIELSNIKENKUNGTDVAVKLIKQELDKYKNA-NH2
374	Ac-SNIKENKUNGTDVAVKLIKQELDKYKNAVTELQLL-NH2
375	Ac-KENKUNGTDVAVKLIKQELDKYKNAVTELQLLMQS-NH2
376	Ac-CLELDKASLWNWFC-NH2
377	Ac-CLELDKASLANWFC-NH2
10 378	Ac-CLELDKASLFNFFC-NH2
379	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKASLFNFF-NH2
381	Ac-RMKQLEDKVEELLSKNYHLENELELDKASLWNWF-NH2
382	Ac-KVEELLSKNYHLENELELDKASLWNWF-NH2
383	Ac-RMKQLEDKVEELLSKLEWIRRSNQKLDISI-NH2
384	Ac-RMKQLEDKVEELLSKLAFIRKSDELLHNV-NH2
385	Ac-ELEALRGELRALRGELELDKASLWNWF-NH2
386	Ac-LDPIDISIELNKAUSDLEESKEWIRRSNQKLDISI-NH2
15 387	Ac-CNEQLSDSFPVEFFQV-NH2
388	Ac-MAEDDPYLGRPEQMFHLDPSL-NH2
389	Ac-EDFSSIADMDFSALLSQISS-NH2
390	Ac-TWQWERKVDFFLEENITALLEEAIQQEKNMYELQ-NH2
391	Ac-WQWERKVDFFLEENITALLEEAIQQEKNMYELQK-NH2
392	Ac-QWERKVDFFLEENITALLEEAIQQEKNMYELQKL-NH2
393	Ac-EWERKVDFFLEENITALLEEAIQQEKNMYELQKLN-NH2
394	Ac-WERKVDFFLEENITALLEEAIQQEKNMYELQKLNS-NH2
20 395	Ac-ERKVDFFLEENITALLEEAIQQEKNMYELQKLNSW-NH2
396	Ac-RKVDFFLEENITALLEEAIQQEKNMYELQKLNSWD-NH2
397	Ac-KVDFFLEENITALLEEAIQQEKNMYELQKLNSWDV-NH2
398	Ac-VDFFLEENITALLEEAIQQEKNMYELQKLNSWDVF-NH2
399	Ac-DFLEENITALLEEAIQQEKNMYELQKLNSWDVFG-NH2
400	Ac-FLEENITALLEEAIQQEKNMYELQKLNSWDVFGN-NH2
401	Ac-LEENITALLEEAIQQEKNMYELQKLNSWDVFGNW-NH2
402	Ac-LEENITALLEEAIQQEKNMYELQKLNSWDVFGNWF-NH2
25 403	Ac-NEQSEKENELYWAKEQLLDLLFNIFNQTVGAWIMQ-NH2
405	Ac-QQQLLDVVKRQQELLRLTVWGTKNLQTRVTAIEKYLKD-NH2
406	Ac-QQLLDVVKRQQELLRLTVWGTKNLQTRVTAIEKYLKDQ-NH2
407	Ac-QQLLDVVKRQQELLRLTVWGPKNLQTRVTAIEKYLKDQ-NH2
408	Ac-DERKQDKVLVVQQTGTLQLTLIQLEKTAKLQWVRLNRY-NH2
409	Ac-QQQLLDVVKRQQELLRLTVWGTKNLQTRVTAIEKY-NH2
410	Ac-QQLLDVVKRQQELLRLTVWGTKNLQTRVTAIEKYL-NH2
411	Ac-QQLLDVVKRQQELLRLTVWGTKNLQTRVTAIEKYLK-NH2
412	Ac-LLDVVKRQQELLRLTVWGTKNLQTRVTAIEKYLKD-NH2
30 413	Ac-LDVVKRQQELLRLTVWGTKNLQTRVTAIEKYLKDQ-NH2
414	Ac-DVVVKRQQELLRLTVWGTKNLQTRVTAIEKYLKDAQ-NH2
415	Ac-VVKRQQELLRLTVWGTKNLQTRVTAIEKYLKDAQ-NH2

T No.	Sequence
416	Ac-VKRQQELLRLTVWGTKNLQTRVTAIEKYLDQAQL-NH2
417	Ac-KRQQELLRLTVWGTKNLQTRVTAIEKYLDQAQLN-NH2
418	Ac-RQQELLRLTVWGTKNLQTRVTAIEKYLDQAQLNA-NH2
419	Ac-QQELLRLTVWGTKNLQTRVTAIEKYLDQAQLNAW-NH2
420	Ac-QELLRLTVWGTKNLQTRVTAIEKYLDQAQLNAWG-NH2
5 421	Ac-ELLRLTVWGTKNLQTRVTAIEKYLDQAQLNAWGC-NH2
422	Ac-NNLLRAIEAQHLLQLTVWGPKQLQARILAVERYLKDQ-NH2
423	Ac-SELEIKRYKNRVASRKCRKFKQLLQHYREVAAAK-NH2
424	Ac-ELEIKRYKNRVASRKCRKFKQLLQHYREVAAAKS-NH2
425	Ac-LEIKRYKNRVASRKCRKFKQLLQHYREVAAAKSS-NH2
426	Ac-EIKRYKNRVASRKCRKFKQLLQHYREVAAAKSSE-NH2
427	Ac-IKRYKNRVASRKCRKFKQLLQHYREVAAAKSSEN-NH2
428	Ac-KRYKNRVASRKCRKFKQLLQHYREVAAAKSSEND-NH2
429	Ac-RYKNRVASRKCRKFKQLLQHYREVAAAKSSENDR-NH2
10 430	Ac-YKNRVASRKCRKFKQLLQHYREVAAAKSSENDRL-NH2
431	Ac-KNRVASRKCRKFKQLLQHYREVAAAKSSENDRLR-NH2
432	Ac-NRVASRKCRKFKQLLQHYREVAAAKSSENDRLRL-NH2
433	Ac-RVASRKCRKFKQLLQHYREVAAAKSSENDRLRLL-NH2
434	Ac-VASRKCRKFKQLLQHYREVAAAKSSENDRLRLLL-NH2
435	Ac-ASRKCRKFKQLLQHYREVAAAKSSENDRLRLLLK-NH2
436	Ac-SRKCRKFKQLLQHYREVAAAKSSENDRLRLLLKQ-NH2
437	Ac-RKCRKFKQLLQHYREVAAAKSSENDRLRLLLKQM-NH2
15 438	Ac-KCRKFKQLLQHYREVAAAKSSENDRLRLLLKQMC-NH2
439	Ac-CRKFKQLLQHYREVAAAKSSENDRLRLLLKQMCP-NH2
440	Ac-RAKFKQLLQHYREVAAAKSSENDRLRLLLKQMCPN-NH2
441	Ac-AKFKQLLQHYREVAAAKSSENDRLRLLLKQMCPSL-NH2
442	Ac-KFKQLLQHYREVAAAKSSENDRLRLLLKQMCPSLD-NH2
443	Ac-FKQLLQHYREVAAAKSSENDRLRLLLKQMCPSLDV-NH2
444	Ac-QQLLQHYREVAAAKSSENDRLRLLLKQMCPSLDVD-NH2
445	Ac-QLLQHYREVAAAKSSENDRLRLLLKQMCPSLDVDS-NH2
20 446	Ac-LLQHYREVAAAKSSENDRLRLLLKQMCPSLDVDSI-NH2
447	Ac-LQHYREVAAAKSSENDRLRLLLKQMCPSLDVDSII-NH2
448	Ac-QHYREVAAAKSSENDRLRLLLKQMCPSLDVDSIIP-NH2
449	Ac-HYREVAAAKSSENDRLRLLLKQMCPSLDVDSIIPR-NH2
450	Ac-YREVAAAKSSENDRLRLLLKQMCPSLDVDSIIPRT-NH2
451	Ac-REVAAAKSSENDRLRLLLKQMCPSLDVDSIIPRTP-NH2
452	Ac-EVAAAKSSENDRLRLLLKQMCPSLDVDSIIPRTPD-NH2
453	Ac-VAAAKSSENDRLRLLLKQMCPSLDVDSIIPRTPDV-NH2
25 454	Ac-AAKSSENDRLRLLLKQMCPSLDVDSIIPRTPDVL-NH2
455	Ac-AAKSSENDRLRLLLKQMCPSLDVDSIIPRTPDVLH-NH2
456	Ac-AKSSENDRLRLLLKQMCPSLDVDSIIPRTPDVLHE-NH2
457	Ac-KSSENDRLRLLLKQMCPSLDVDSIIPRTPDVLHED-NH2
458	Ac-SSENDRLRLLLKQMCPSLDVDSIIPRTPDVLHEDL-NH2
459	Ac-SENDRLRLLLKQMCPSLDVDSIIPRTPDVLHEDLL-NH2
460	Ac-ENDRLRLLLKQMCPSLDVDSIIPRTPDVLHEDLLN-NH2
461	Ac-NDRLRLLLKQMCPSLDVDSIIPRTPDVLHEDLLNF-NH2
30 534	Ac-PGYRWMCLRRFIIIFLIFILLCLIFLLVLLDYQGML-NH2
535	Ac-GYRWMCLRRFIIIFLIFILLCLIFLLVLLDYQGMLP-NH2
536	Ac-YRWMCLRRFIIIFLIFILLCLIFLLVLLDYQGMLPV-NH2
537	Ac-RWMCLRRFIIIFLIFILLCLIFLLVLLDYQGMLPVC-NH2

T	No.	Sequence
	538	AC-WMCLRRFIIIFLFILLLLCLIFLLVLLDYQGMLPVCPL-NH2
	539	AC-MCLRRFIIIFLFILLLLCLIFLLVLLDYQGMLPVCPL-NH2
	540	AC-CLRRFIIIFLFILLLLCLIFLLVLLDYQGMLPVCPLI-NH2
	541	AC-LRRFIIIFLFILLLLCLIFLLVLLDYQGMLPVCPLIP-NH2
	542	AC-RRFIIIFLFILLLLCLIFLLVLLDYQGMLPVCPLIPG-NH2
5	543	AC-RFIIIFLFILLLLCLIFLLVLLDYQGMLPVCPLIPGS-NH2
	544	AC-FIIFLFILLLLCLIFLLVLLDYQGMLPVCPLIPGSS-NH2
	545	AC-IIIFLFILLLLCLIFLLVLLDYQGMLPVCPLIPGSST-NH2
	546	AC-IFLFILLLLCLIFLLVLLDYQGMLPVCPLIPGSSTT-NH2
	547	AC-FLFILLLLCLIFLLVLLDYQGMLPVCPLIPGSSTTS-NH2
	548	AC-LFILLLLCLIFLLVLLDYQGMLPVCPLIPGSSTTST-NH2
	549	AC-FILLLLCLIFLLVLLDYQGMLPVCPLIPGSSTTSTG-NH2
	550	AC-ILLLLCLIFLLVLLDYQGMLPVCPLIPGSSTTSTGP-NH2
	551	AC-LLLCLIFLLVLLDYQGMLPVCPLIPGSSTTSTGPC-NH2
10	552	AC-LCLIFLLVLLDYQGMLPVCPLIPGSSTTSTGPCR-NH2
	553	AC-LCLIFLLVLLDYQGMLPVCPLIPGSSTTSTGPCRTC-NH2
	554	AC-CLIFLLVLLDYQGMLPVCPLIPGSSTTSTGPCRTC-NH2
	555	AC-LIFLLVLLDYQGMLPVCPLIPGSSTTSTGPCRTCM-NH2
	556	AC-IFLLVLLDYQGMLPVCPLIPGSSTTSTGPCRTCMT-NH2
	557	AC-FLLVLLDYQGMLPVCPLIPGSSTTSTGPCRTCMTT-NH2
	558	AC-PPLVLQAGFFLLTRILTIPQSLDSWWTSLNFLGGT-NH2
	559	AC-LLVLQAGFFLLTRILTIPQSLDSWWTSLNFLGGTT-NH2
15	560	AC-LVLQAGFFLLTRILTIPQSLDSWWTSLNFLGGTTV-NH2
	561	AC-VLQAGFFLLTRILTIPQSLDSWWTSLNFLGGTTVC-NH2
	562	AC-LQAGFFLLTRILTIPQSLDSWWTSLNFLGGTTVCL-NH2
	563	AC-QAGFFLLTRILTIPQSLDSWWTSLNFLGGTTVCLG-NH2
	564	AC-AGFFLLTRILTIPQSLDSWWTSLNFLGGTTVCLGQ-NH2
	565	AC-GFFLLTRILTIPQSLDSWWTSLNFLGGTTVCLGQN-NH2
	566	AC-FFLLTRILTIPQSLDSWWTSLNFLGGTTVCLGQNS-NH2
	567	AC-FLLTRILTIPQSLDSWWTSLNFLGGTTVCLGQNSQ-NH2
20	568	AC-LLTRILTIPQSLDSWWTSLNFLGGTTVCLGQNSQS-NH2
	569	AC-LTRILTIPQSLDSWWTSLNFLGGTTVCLGQNSQSP-NH2
	570	AC-FWNWLSAWKDLELKSLLLEVKDELQKMR-NH2
	571	AC-NNLLRAIEAQHLLQLTVW-NH2
	572	AC-CGGNNLLRAIEAQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
	573	AC-YTSLIHSLIEESQNQQEKNEQEELLELDKASLWNWF-NH2
	574	C13H27CO-YTSLIHSLIEESQNQQEKNEQEELLELDKASLWNWF-NH2
	575	AC-AVSKGYLSALRTGWYTSVITIELSNIKENKUNGTD-NH2
25	576	AC-SISNIETVIEFQQKNRLLLEITREFSVNAGVTTPVS-NH2
	577	AC-DQQIKQYKRLLDRLIIPLYDGLRQKDVIVSNQESN-NH2
	578	AC-YSELTNIFGDNIGSLQEKGIKLGQIASLYRTNITEI-NH2
	579	AC-TSITLQVRLPLLTRLNLTQIYRVDSISYNIQNREWY-NH2
	580	AC-VEIAEYRLLRTVLEPIRDALNMTQNIIRPVQSVA-NH2
	581	AC-SYFIVLSIAYPTLSEIKGVIVHRLEGVSYNIGSQEW-NH2
	582	AC-LKEAIRDNTKAVQSVQSSIGNLIVAIS-NH2
	583	NNLLRAIEAQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
	583	NNLLRAIEAQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
30	584	QKQEPIDKELYPLTSL
	585	YPKFVKQNTLKLAT
	586	QYIKANQKFIGITE

T	No.	Sequence
	587	NGQIGNDPNDRDILY
	588	AC-RPDVY-OH
	589	CLELDKWASLWNNWFC- (cyclic)
	590	CLELDKWASLANWFC- (cyclic)
	591	CLELDKWASLANFFC- (cyclic)
5	594	Ac-NNLLRAIEAQQQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
	595	Ac-CGGYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNNWF-NH2
	596	Ac-PLLVLQAGFFLLTRILTIPQSLDSWWTSLNFLGGT-NH2
	597	Ac-LLVLQAGFFLLTRILTIPQSLDSWWTSLNFLGGTT-NH2
	598	Ac-LVLQAGFFLLTRILTIPQSLDSWWTSLNFLGGTTV-NH2
	599	Ac-VLQAGFFLLTRILTIPQSLDSWWTSLNFLGGTTVC-NH2
	600	Ac-LQAGFFLLTRILTIPQSLDSWWTSLNFLGGTTVCL-NH2
	601	Ac-QAGFFLLTRILTIPQSLDSWWTSLNFLGGTTVCLG-NH2
	602	Ac-AGFFLLTRILTIPQSLDSWWTSLNFLGGTTVCLGQ-NH2
10	603	Ac-GFFLLTRILTIPQSLDSWWTSLNFLGGTTVCLGQN-NH2
	604	Ac-FFLLTRILTIPQSLDSWWTSLNFLGGTTVCLGQNS-NH2
	605	Ac-FLLTRILTIPQSLDSWWTSLNFLGGTTVCLGQNSQ-NH2
	606	Ac-LLTRILTIPQSLDSWWTSLNFLGGTTVCLGQNSQS-NH2
	607	Ac-LTRILTIPQSLDSWWTSLNFLGGTTVCLGQNSQSP-NH2
	608	Ac-LELDKWASLWNNWA-NH2
	609	Ac-LELDKWASAWNWF-NH2
	610	Ac-LELDKAASLWNNWF-NH2
15	611	Ac-LKLDKWASLWNNWF-NH2
	612	Ac-LELKKWASLWNNWF-NH2
	613	Ac-DELLHNVNAGKST-NH2
	614	Ac-KSDELLHNVNAGKST-NH2
	615	Ac-IRKSDELLHNVNAGKST-NH2
	616	Ac-AFIRKSDELLHNVNAGKST-NH2
	617	Ac-FDASISQVNEKINQSLAFI-NH2
	618	Ac-YAADKESTQKAFDGITNKVNSVIEKMNTQFEAVGKE-NH2
20	619	Ac-SVIEKMNTQFEAVGKEFGNLERLENLNKRMEDGFL-NH2
	620	Ac-VWTYNALLVLMENERTLDFHDSNVKNLYDKVRMQL-NH2
	621	Ac-EWDREINNYTSLIHSLIEESQNQQEKNEQEGGC-NH2
	622	Ac-INNYTSLIHSLIEESQNQQEKNEQELLELDKWASL-NH2
	623	Ac-INNYTSLIHSLIEESQNQQEKNEQELLE-NH2
	624	Ac-WMEWDREINNYTSLIHSLIEESQNQQEKNEQELLE-NH2
	625	Ac-MTWMEWDREINNYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNNWF-NH2
	626	Ac-IDISIELNKAUSDLEESKEWIKSNQKLDSIGNWH-NH2
25	627	Ac-NQQEKNEQELLELDKWASLWNNWFNITNWLWYIKIFI-NH2
	627	Ac-NQQEKNEQELLELDKWASLWNNWFNITNWLWYIKIFI-NH2
	628	Ac-QNQEKNEQELLELDKWASLWNNWFNITNWLWYIKIFI-NH2
	629	Ac-SQNQQEKNEQELLELDKWASLWNNWFNITNWLWYIKI-NH2
	630	Ac-ESQNQQEKNEQELLELDKWASLWNNWFNITNWLWYIKI-NH2
	631	Ac-EESQNQQEKNEQELLELDKWASLWNNWFNITNWLWYI-NH2
	632	Ac-IEESQNQQEKNEQELLELDKWASLWNNWFNITNWLWYI-NH2
	633	Ac-LIEESQNQQEKNEQELLELDKWASLWNNWFNITNWLW-NH2
	634	Ac-SLIEESQNQQEKNEQELLELDKWASLWNNWFNITNWL-NH2
30	635	Ac-HSLIEESQNQQEKNEQELLELDKWASLWNNWFNITN-NH2
	636	Ac-IHSLIEESQNQQEKNEQELLELDKWASLWNNWFNITN-NH2
	637	Ac-LIHSLIEESQNQQEKNEQELLELDKWASLWNNWFNIT-NH2

T No.	Sequence
638	Ac-SLIHSLIEESQNQQEKNEQELLELDKWASLWNWFI-NH2
639	Ac-TSLIHSLIEESQNQQEKNEQELLELDKWASLWNWFI-NH2
640	Ac-NYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNW-NH2
641	Ac-MNYTSLIHSLIEESQNQQEKNEQELLELDKWASLWN-NH2
642	Ac-INNYTSLIHSLIEESQNQQEKNEQELLELDKWASLW-NH2
643	Ac-EINNYTSLIHSLIEESQNQQEKNEQELLELDKWASL-NH2
5 644	Ac-REINNYTSLIHSLIEESQNQQEKNEQELLELDKWAS-NH2
645	Ac-DREINNYTSLIHSLIEESQNQQEKNEQELLELDKWA-NH2
646	Ac-WDREINNYTSLIHSLIEESQNQQEKNEQELLELDKW-NH2
647	Ac-EWDREINNYTSLIHSLIEESQNQQEKNEQELLELDK-NH2
648	Ac-MEWDREINNYTSLIHSLIEESQNQQEKNEQELLELD-NH
649	Ac-WMEWDREINNYTSLIHSLIEESQNQQEKNEQELLELD-NH2
650	Ac-TWMEWDREINNYTSLIHSLIEESQNQQEKNEQELLE-NH2
651	Ac-MTWMEWDREINNYTSLIHSLIEESQNQQEKNEQELL-NH2
10 652	Ac-NMTWMEWDREINNYTSLIHSLIEESQNQQEKNEQEL-NH2
653	Ac-NNMTWMEWDREINNYTSLIHSLIEESQNQQEKNEQE-NH2
654	Ac-WNNMTWMEWDREINNYTSLIHSLIEESQNQQEKNEQ-NH2
655	Ac-IWNNMTWMEWDREINNYTSLIHSLIEESQNQQEKNE-NH2
656	Ac-QIWNNMTWMEWDREINNYTSLIHSLIEESQNQQEKN-NH2
657	Ac-EQIWNNMTWMEWDREINNYTSLIHSLIEESQNQQEK-NH2
658	Ac-LEQIWNNMTWMEWDREINNYTSLIHSLIEESQNQQE-NH2
659	Ac-SLEQIWNNMTWMEWDREINNYTSLIHSLIEESQNQQ-NH2
15 660	Ac-KSLEQIWNNMTWMEWDREINNYTSLIHSLIEESQNQ-NH2
661	Ac-NKSLEQIWNNMTWMEWDREINNYTSLIHSLIEESQN-NH2
662	Ac-SLAFIRKSDDELLHNVNAGKST-NH2
663	Ac-FDASISQVNEKINQSLAFIRK-NH2
664	Ac-YTSLIHSLIEESQQQEKQEQELLELDKWASLWNWF-NH2
665	Ac-FDASISQVNEKINQSLAFIRKSDDELLHNVNAGK-NH2
666	Ac-FDASISQVNEKINQSLAFIRKSDDELLHNVNA-NH2
667	Ac-FDASISQVNEKINQSLAFIRKSDDELLHNV-NH2
20 668	Ac-FDASISQVNEKINQSLAFIRKSDDELLH-NH2
669	Ac-FDASISQVNEKINQSLAFIRKSDDEL-NH2
670	Ac-FDASISQVNEKINQSLAFIRKSD-NH2
671	Ac-ASISQVNEKINQSLAFIRKSDDELLHNVNAGKST-NH2
672	Ac-ISQVNEKINQSLAFIRKSDDELLHNVNAGKST-NH2
673	Ac-QVNEKINQSLAFIRKSDDELLHNVNAGKST-NH2
674	Ac-NEKINQSLAFIRKSDDELLHNVNAGKST-NH2
675	Ac-KINQSLAFIRKSDDELLHNVNAGKST-NH2
25 676	Ac-NQSLAFIRKSDDELLHNVNAGKST-NH2
677	Ac-FWNWLSAWKDLELYPGSLELDKWASLWNWF-NH2
678	Ac-CGGNNLLRAIEAQOHLQLTVWGIKQLQARILAVERYLKDQ-NH2
679	Ac-CGGYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
680	YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF
681	NNLLRAIEAQOHLQLTVWGIKQLQARILAVERYLKDQ
682	Ac-EKNMYELQKLNSWDVFTNWLDFTSWVRYIQYIQYGV-NH2
683	Ac-QEKNMYELQKLNSWDVFTNWLDFTSWVRYIQYIQYG-NH2
684	Ac-QQEKMYELQKLNSWDVFTNWLDFTSWVRYIQYIQY-NH2
30 685	Ac-IQQEKMYELQKLNSWDVFTNWLDFTSWVRYIQYIQ-NH2
686	Ac-QIQQEKMYELQKLNSWDVFTNWLDFTSWVRYIQYI-NH2
687	Ac-AQIQQEKMYELQKLNSWDVFTNWLDFTSWVRYIQY-NH2

T	No.	Sequence
	688	Ac-QAQIQQEKMYELQKLNSWDVFTNWLDFTSWVRYIQ-NH2
	689	Ac-EQAQIQQEKMYELQKLNSWDVFTNWLDFTSWVRYI-NH2
	690	Ac-LEQAQIQQEKMYELQKLNSWDVFTNWLDFTSWVRY-NH2
	691	Ac-SLEQAQIQQEKMYELQKLNSWDVFTNWLDFTSWVR-NH2
	692	Ac-QSLEQAQIQQEKMYELQKLNSWDVFTNWLDFTSWV-NH2
5	693	Ac-SQSLEQAQIQQEKMYELQKLNSWDVFTNWLDFTSW-NH2
	694	Ac-ISQSLEQAQIQQEKMYELQKLNSWDVFTNWLDFTS-NH2
	695	Ac-NISQSLEQAQIQQEKMYELQKLNSWDVFTNWLDFT-NH2
	696	Ac-ANISQSLEQAQIQQEKMYELQKLNSWDVFTNWLD-NH2
	697	Ac-EANISQSLEQAQIQQEKMYELQKLNSWDVFTNWLD-NH2
	699	Ac-YLEANISQSLEQAQIQQEKMYELQKLNSWDVFTNW-NH2
	700	Ac-YTSLIHSLIEESQNQQEKNEQEL-NH2
	701	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	702	Ac-YTSLIHSLIEESQNQQEKLEQELLELDKWASLWNWF-NH2
10	703	Ac-YTSLIHSLIEESQNQQEKNEQELLEFDKWASLWNWF-NH2
	704	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKPASLWNWF-NH2
	705	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	706	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNSF-NH2
	707	Biotin NH (CH ₂) ₄ CO-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	708	Biotin NH (CH ₂) ₆ CO-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	709	FMOC-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF
	710	FMOC-NNLLRAIEAQHLLQLTVWGIKQLQARILAVERYLKDQ
15	711	Ac-EWDREINNYTSLIHSLIEESQNQQEKNEQE-NH2
	712	Ac-LIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	713	Ac-FWNWLSAWKDLELGGPGSGPGLELDKWASLWNWF-NH2
	714	Ac-LIHSLIEESQNQQEKNEQELLELDKWASL-NH2
	715	Ac-TSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	716	Ac-LIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	718	FMOC-GGGGGYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	719	Ac-HSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
20	720	Ac-YTSLIYSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	721	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	722	Ac-YTSLIHSSIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	723	Ac-LEANISQLLEQAQIQQEKMYELQKLNSWDVFTNW-NH2
	724	Ac-SLEECDSELEIKRYKNRVASRKCRKFKQLLQHYR-NH2
	725	Ac-LEECDSELEIKRYKNRVASRKCRKFKQLLQHYRE-NH2
	726	Ac-EECDSELEIKRYKNRVASRKCRKFKQLLQHYREV-NH2
	727	Ac-ECDSELEIKRYKNRVASRKCRKFKQLLQHYREVA-NH2
25	728	Ac-CDSELEIKRYKNRVASRKCRKFKQLLQHYREVAA-NH2
	729	Ac-DSELEIKRYKNRVASRKCRKFKQLLQHYREVAAA-NH2
	730	Desaminotyrosine-FDASISQVNEKINQSLAFIRKSDELLHNVNAGKST-NH2
	731	WASLWNW-NH2
	732	Ac-EAQHLLQLTVWGIKQLQARILAVERYLKDQQLLGIW-NH2
	733	Ac-IEAQHLLQLTVWGIKQLQARILAVERYLKDQQLGIW-NH2
	734	Ac-AIEAQHLLQLTVWGIKQLQARILAVERYLKDQQLGI-NH2
	735	Ac-RAIEAQHLLQLTVWGIKQLQARILAVERYLKDQQLGI-NH2
	736	Ac-LRAIEAQHLLQLTVWGIKQLQARILAVERYLKDQQL-NH2
30	737	Ac-LLRAIEAQHLLQLTVWGIKQLQARILAVERYLKDQQL-NH2
	738	Ac-NLLRAIEAQHLLQLTVWGIKQLQARILAVERYLKDQQL-NH2
	739	Ac-QNNLLRAIEAQHLLQLTVWGIKQLQARILAVERYLKD-NH2

T No.	Sequence
740	Ac-QQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLK-NH2
741	Ac-QQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYL-NH2
742	Ac-VQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERY-NH2
743	Ac-IVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVER-NH2
744	Ac-GIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVE-NH2
745	Ac-SGIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAV-NH2
5 758	Ac-RSMTLTQARQLLSGIVQQQNNLLRAIEAQQHLLQLTV-NH2
760	Ac-GARSMTLTQARQLLSGIVQQQNNLLRAIEAQQHLLQL-NH2
764	Ac-GSTMGARSMTLTQARQLLSGIVQQQNNLLRAIEAQQH-NH2
765	Ac-GSTMGARSMTLTQARQLLSGIVQQQNNLLRAIEAQQH-NH2
766	Ac-EGSTMGARSMTLTQARQLLSGIVQQQNNLLRAIEAQQ-NH2
767	Ac-RAKFKQLLQHYREVAAAKSSENDRLRLL-NH2
768	Ac-AKFKQLLQHYREVAAAKSSENDRLRLLL-NH2
769	Ac-KFKQLLQHYREVAAAKSSENDRLRLLK-NH2
10 770	Ac-FKQLLQHYREVAAAKSSENDRLRLLKQ-NH2
771	Ac-RAKFKQELQHYREVAAAKSSENDRLRLLKQMCP-S-NH2
772	DKWASLWNWF-NH2
773	Biotin-FDASISQVNEKINQSLAFIRKSDELLHNVNAGKST-NH2
774	Ac-YDASISQVNEKINQSLAFIRKSDELLHNVNAGKST-NH2
775	Ac-YDASISQVNEKINQSLAYIRKSDELLHNVNAGKST-NH2
776	Ac-FDASISQVNEKINQSLAYIRKSDELLHNVNAGKST-NH2
777	Ac-FDASISQVQEKIQSLAFIRKSDELLHQVQAGKST-NH2
15 778	Ac-FDASISQVNEKINQALAFIRKADELHNVNAGKST-NH2
779	Ac-FDASISQVNEKINQALAFIRKSDELLHNVNAGKST-NH2
780	Ac-FDASISQVNEKINQSLAFIRKADELHNVNAGKST-NH2
781	Ac-YDASISQVQEEIQALAFIRKADELLEQVQAGKST-NH2
782	Ac-FDASISQVNEKINQSLAFIRKSDELLENVNAGKST-NH2
783	Ac-FDASISQVNEEINQSLAFIRKSDELLHNVNAGKST-NH2
784	Ac-VFPSDEFDASISQVNEKINQSLAFIRKSDELLENV-NH2
785	Ac-VFPSDEFDASISQVNEEINQSLAFIRKSDELLENV-NH2
20 786	Ac-VYPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
787	Ac-VFPSDEFDASISQVNEEINQSLAFIRKSDELLHNV-NH2
788	Ac-SNKSLEQIWNMTWMEWDREINNYTSLIHSLIEESQ-NH2
789	Ac-WSNKSLEQIWNMTWMEWDREINNYTSLIHSLIEES-NH2
790	Ac-SWSNKSLEQIWNMTWMEWDREINNYTSLIHSLIEE-NH2
791	Ac-ASWSNKSLEQIWNMTWMEWDREINNYTSLIHSLIE-NH2
792	Ac-NASWSNKSLEQIWNMTWMEWDREINNYTSLIHSLI-NH2
793	Ac-WNASWSNKSLEQIWNMTWMEWDREINNYTSLIHSL-NH2
25 793	Ac-WNASWSNKSLEQIWNMTWMEWDREINNYTSLIHSL-NH2
794	Ac-PWNASWSNKSLEQIWNMTWMEWDREINNYTSLIHS-NH2
795	Ac-VPWNASWSNKSLEQIWNMTWMEWDREINNYTSLIH-NH2
796	Ac-AVPWNASWSNKSLEQIWNMTWMEWDREINNYTSLI-NH2
797	Ac-TAVPWNASWSNKSLEQIWNMTWMEWDREINNYTSL-NH2
798	Ac-TTAVPWNASWSNKSLEQIWNMTWMEWDREINNYTS-NH2
800	Ac-AAASDEFDASISQVNEKINQSLAFIRKSDELLHNV-NH2
801	Ac-VFPAAAFDASISQVNEKINQSLAFIRKSDELLHNV-NH2
802	Ac-VFPSDEAAAASISQVNEKINQSLAFIRKSDELLHNV-NH2
30 803	Ac-VFPSDEFDAAAAQVNEKINQSLAFIRKSDELLHNV-NH2
804	Ac-VFPSDEFDASISAAAEKINQSLAFIRKSDELLHNV-NH2
805	Ac-VFPSDEFDASISQVNAANQSLAFIRKSDELLHNV-NH2

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	806	Ac-VFPSDEFDASISQVNEKIAAALAFIRKSDELLHNV-NH2
	807	Ac-VFPSDEFDASISQVNEKINQSAAAIRKSDELLHNV-NH2
	808	Ac-VFPSDEFDASISQVNEKINQSLAFAAASDELLHNV-NH2
	809	Ac-VFPSDEFDASISQVNEKINQSLAFIRKAAALLHNV-NH2
	810	Ac-VFPSDEFDASISQVNEKINQSLAFIRKSDEAAANV-NH2
5	811	Ac-VFPSDEFDASISQVNEKINQSLAFIRKSDELLAAA-NH2
	812	Ac-VFPSDEFDASISQVNEKINQSLAFIRKSDELLHNV-NH2
	813	Ac-AAAAIHSLIEESQNQQEKNEQEELLELDKWASLWNWF-NH2
	814	Ac-YTSLIHSLIEESQNQQEKNEQEELLELDKWASLWNWF-NH2
	815	Ac-YTSLIHSLIEESQNQQEKNEQEELLELDKWASLWNWF-NH2
	816	Ac-QIWNMTWMEWDREINNYTSLIHSLIEESQNQQEKQ-NH2
	817	Ac-QIWNMTWMEWDREINNYTSLIHSLIEESQNQQEKN-NH2
	818	Ac-QIWNMTWMEWDREINNYTSLIHSLIEESQNQQEKQ-NH2
	819	Ac-NKSLEQIWNMTWMEWDREINNYTSLIHSLIEESQQ-NH2
10	820	Ac-FDASISQVNEKINQSLAFIEESDELLHNVNAGKST-NH2
	821	Ac-ACIRKSDELCL-NH2
	823	Ac-YTSLIHSLIEESQNQQEKDEQEELLELDKWASLWNWF-NH2
	824	Ac-YTSLIHSLIEESQDQQEKNEQEELLELDKWASLWNWF-NH2
	825	Ac-YTSLIHSLIEESQDQQEKDEQEELLELDKWASLWNWF-NH2
	826	Ac-YTSLIHSLIEESQNQQEKNEQEELLELDKWASLWDF-NH2
	841	Ac-LEANITQSLEQAQIQQEKMYELQKLNSWDVFTNWL-NH2
	842	Ac-LEANISASLEQAQIQQEKMYELQKLNSWDVFTNWL-NH2
15	843	Ac-LEANISALLEQAQIQQEKMYELQKLNSWDVFTNWL-NH2
	844	Ac-LEANITALLEQAQIQQEKMYELQKLNSWDVFTNWL-NH2
	845	Ac-LEANITASLEQAQIQQEKMYELQKLNSWDVFTNWL-NH2
	845	Ac-LEANITASLEQAQIQQEKMYELQKLNSWDVFTNWL-NH2
	846	Ac-RAKFKQLLQHYREVAAAKSENDRLRLLLKQMUPS-NH2
	847	Ac-Abu-DDE-Abu-MNSVKNGTYDYPKYEESKLNREIKGVKL-NH2
	856	Ac-WQEWQKVRYLEANISQSLEQAQIQQEKMYELQKL-NH2
	860	Ac-DEYDASISQVNEKINQSLAFIRKSDELLHNVNAGK-NH2
20	861	Ac-YTSLIHSLIEESQNQQEKNEQEELLELDKWASLWN-NH2
	862	Ac-YTSLIHSLIEESQNQQEKNEQEELLELDKWASLW-NH2
	863	Ac-YTSLIHSLIEESQNQQEKNEQEELLELDKWASL-NH2
	864	Ac-YTSLIHSLIEESQNQQEKNEQEELLELDKWAS-NH2
	865	Ac-QARQLLSGIVQQNNLLRAIEAQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
	866	Ac-DREINNYTSLIHSLIEESQNQQEKNEQEELLELDKWASLWNWF-NH2
	867	Ac-NNMTWMEWDREINNYTSLIHSLIEESQNQQEKNEQEELLELDK-NH2
	868	Ac-YTSLIHSLIEESQNQQEKNEQEELLELDKWASLWAAA-NH2
25	869	Ac-YTSLIHSLIEESQNQQEKNEQEELLELDKWAAAANWF-NH2
	870	Ac-YTSLIHSLIEESQNQQEKNEQEELLELDAAASLWNWF-NH2
	871	Ac-YTSLIHSLIEESQNQQEKNEQEELAAAKWASLWNWF-NH2
	872	Ac-YTSLIHSLIEESQNQQEKNEQAAAELELDKWASLWNWF-NH2
	873	Ac-YTSLIHSLIEESQNQQEKAAAELELDKWASLWNWF-NH2
	874	Ac-YTSLIHSLIEESQNQAAANEQEELLELDKWASLWNWF-NH2
	875	Ac-YTSLIHSLIEESAAAEKNEQEELLELDKWASLWNWF-NH2
	876	Ac-YTSLIHSLIAAQNQQEKNEQEELLELDKWASLWNWF-NH2
	877	Ac-YTSLIHAAAEESQNQQEKNEQEELLELDKWASLWNWF-NH2
30	878	Ac-YTSAAASLIEESQNQQEKNEQEELLELDKWASLWNWF-NH2
	879	Ac-EIWNMTWMEWDRENEKINQSLAFIRKSDELLHNV-NH2
	880	Ac-YISEVNEEINQSLAFIRKADELLENVDKWASLWNWF-NH2

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	881	Ac-TSVITIELSNIKENKANGTDAKVKLIKQELDKYKN-NH2
	882	YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWFMG-NH2
	883	Ac-NEKINQSLAFIRKSDELHNV-NH2
	884	Biotin-YDPLVFPSDEFDASISQVNEKINQSLAFIRKSDEL-NH2
	885	Biotin-PLVFPSPDEFDASISQVNEKINQSLAFIRKSDELLH-NH2
5	886	Biotin-VFPSDEFDASISQVNEKINQSLAFIRKSDELHNV-NH2
	887	Biotin-DEFDASISQVNEKINQSLAFIRKSDELHNVNAGK-NH2
	888	Biotin-VYPSDEFDASISQVNEKINQSLAFIRKSDELHNV-NH2
	889	Biotin-VYPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
	890	Ac-VYPSDEFDASISQVQEEIQQALAFIRKADELLEQV-NH2
	891	Ac-NYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	892	Ac-NNYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	893	Ac-INNYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	894	Ac-EINNYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
10	895	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWFN-NH2
	896	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWFNI-NH2
	897	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWFNIT-NH2
	898	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWFNITN-NH2
	899	Ac-YDPLVFPSDEFDASISQVNEKINQSLAFIRKSDELHNVNAGK-NH2
	900	Ac-NYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWFN-NH2
	901	Ac-NNYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWFNI-NH2
	905	Ac-KCRKFKQLLQHYREVAAKSSSENDRLRLLKQMCPSLDVDSIIPRTPD-NH2
15	906	Ac-RAKFKQLLQHYREVAAKSSSENDRLRLLKQMCPSLDVDSIIPRTPD-NH2
	907	Ac-VYPSDEYDASISQVNEEINQALAYIAADELLENV-NH2
	909	Ac-YDASISQVNEEINQALAYIRKADELL-NH2
	910	Ac-M-Nle-WMEWDREINNYTSLIHSLIEESQNQQEKNEQELLELD-NH2
	911	Ac-KNGTYDYPKYEEESKLRNEIKGVKLSSMGVYQI-NH2
	912	Ac-VTEKIQMASDNINDLIQSGVNTRLTLTIQSHVQNYI-NH2
	913	QNQQEKNEQELLELDKWASLWNWF-NH2
	914	Ac-QNQQEKNEQELLELDKWASLWNWF-NH2
20	915	LWNWF-NH2
	916	ELLELDKWASLWNWF-NH2
	917	EKNEQELLELDKWASLWNWF-NH2
	918	SLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	919	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNW
	920	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWN
	921	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASIW
	922	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASL
25	923	TSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	924	SLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	925	LIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	926	IHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	940	Ac-AAVALLPAVLLALLAPSELEIKRYKNRVASRKCRAKFKQLLQHYREVAAK-NH2
	941	Ac-AAVALLPAVLLALLAPCRAKFKQLLQHYREVAAKSSSENDRLRLLKQMCN-NH2
	942	Ac-YTSLIHSLIEESQNQQEKNNNIEDWEMWTMNNWQ-NH2
	944	VYPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
	945	Ac-LMQLARQLMQLARQMKQLADSLMQLARQVSRLESA-NH2
30	946	Ac-WMEWDREINNYTSLIHSLIEESQNQQEKNEQELLELD-NH2
	947	Ac-MEWDREINNYTSLIHSLIEESQNQQEKNEQELLELD-NH2
	948	Ac-EWDREINNYTSLIHSLIEESQNQQEKNEQELLELD-NH2

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	949	Ac-MEWDREINNYTSLIHSLIEESQNQQEKNEQEELLE-NH2
	950	Biotin-W-Nle-EWDREINNYTSLIHSLIEESQNQQEKNEQEELLE-NH2
	951	Ac-YLEYDREINNYTSLIHSLIEESQNQQEKNEQEELLE-NH2
	952	Ac-IKQFINMWQEVGKAMYA-NH2
	953	Ac-IRKSDELL-NH2
5	954	Decanoyl-IRKSDELL-NH2
	955	Acetyl-Aca-Aca-IRKSDELL-NH2
	956	Ac-YDASISQV-NH2
	957	Ac-NEKINQSL-NH2
	958	Ac-SISQVNEEINQALAYIRKADELL-NH2
	959	Ac-QVNEEINQALAYIRKADELL-NH2
	960	Ac-EEINQALAYIRKADELL-NH
	961	Ac-NQALAYIRKADELL-NH2
	962	Ac-LAYIRKADELL-NH2
10	963	FDASISQVNEKINQALAFIRKSDELL-NH2
	964	Ac-W-Nle-EWDREINNYTSLIHSLIEESQNQQEKNEQEELLE-NH2
	965	Ac-ASRKCRKFKQLLQHYREVAAKSSENDRLRLLLKQMCPSLDVDS-NH2
	966	Ac-WLEWDREINNYTSLIHSLIEESQNQQEKNEQEELLE-NH2
	967	Ac-YVKGEPITINFYDPLVFPSEDFDASISQVNEKINQSL-NH2
	968	Ac-VYPSDEYDASISQVNEEINQSLAYIRKADELLHNV-NH2
	969	Ac-YDASISQVNEEINQALAYIRKADELLENV-NH2
	970	Ac-YDASISQVNEEINQALAYIRKADELLE-NH2
15	971	Ac-YDASISQVNEEINQALAYIRKADELLE-NH2
	972	Ac-VYPSDEYDASISQVNEEINQALAYIRKAAELLHNV-NH2
	973	Ac-VYPSDEYDASISQVNEEINQALAYIRKALELLHNV-NH2
	974	Decanoyl-YTSLIHSLIEESQNQQEKNEQEELLELDKASLWNWF-NH2
	975	Ac-VYPSDEYDASISQVNEEINQLLAYIRKLDELLENV-NH2
	976	Ac-DEYDASISQVNEKINQSLAFIRKSDELL-NH2
	977	Ac-SNDQSGYAADKESTQKAFDGITNKVNSVIEKTNT-NH2
	978	Ac-ESTQKAFDGITNKVNSVIEKTNTQFEAVGKEFGNLEKR-NH2
	979	Ac-DGITNKVNSVIEKTNTQFEAVGKEFGNLEKRLENLNK-NH2
20	980	Ac-DSNVKNLYDKVRSQLRDNVKELGNGAFEFYHK-NH2
	981	Ac-RDNVKELGNGAFEFYHKADDEALNSVKNGTYPKY-NH2
	982	Ac-EFYHKADDEALNSVKNGTYPKY-NH2
	983	Ac-AAVALLPAVLLALLAPAADKESTQKAFDGITNKVNS-NH2
	984	Ac-AAVALLPAVLLALLAPAADSNVKNLYDKVRSQLRDN-NH2
	985	Ac-KESTQKAFDGITNKVNSV-NH2
	986	Ac-IEKTNTQFEAVGKEFGNLER-NH2
	987	Ac-RLENLNKRVEDGFLDVWTYNAELLVALENE-NH2
25	988	Ac-SNVKNLYDKVRSQLRDN-NH2
	989	Ac-WMEWDREINNYTSLIHSLIEESQNQQEKNEQEL-NH2
	990	Ac-WMEWDREINNYTSLIHSLIEESQNQQEKNEQE-NH2
	991	Ac-MEWDREINNYTSLIHSLIEESQNQQEKNEQEL-NH2
	992	Ac-MEWDREINNYTSLIHSLIEESQNQQEKNEQE-NH2
	993	Ac-EWDREINNYTSLIHSLIEESQNQQEKNEQEELLE-NH2
	994	Ac-EWDREINNYTSLIHSLIEESQNQQEKNEQELL-NH2
	995	Ac-EWDREINNYTSLIHSLIEESQNQQEKNEQEL-NH2
30	996	Ac-YTKFIYTLLEESQNQQEKNEQEELLELDKASLWNWF-NH2
	997	Ac-YMKQLADSLMQLARQVSRLESA-NH2
	998	Ac-YLMQLARQMKQLADSLMQLARQVSRLESA-NH2
	999	Ac-YQWERKVDLFLEENITALLEEAQIQQEKNMVELQKL-NH2

T	No.	Sequence
	1000	Ac-WMAWAAAINNYTSLIHSLIEESQNQQEKNEQEEL-EE-NH2
	1001	Ac-YASLIAALIEESQNQQEKNEQEEL-ELAKWAALWAWF-NH2
	1002	[Ac-EWDREINNYTSLIHSLIEESQNQQEKNEQEGGC-NH2] dimer
	1003	Ac-YDISIELNKAQSDLEESKEWIKKSNQKLD SIGNWH-NH2
	1004	Biotinyl-IDISIELNKAQSDLEESKEWIKKSNQKLD SIGNWH-NH2
5	1005	Ac-YTSLI-OH
	1006	Fmoc-HSLIEE-OH
	1007	Fmoc-SQNQQEK-OH
	1008	Fmoc-NEQEEL-EL-OH
	1009	Fmoc-DKWASL-OH
	1010	Fmoc-WNWF-OH
	1011	Ac-AKTLERTWDTLNLHLLFISSALYKLNKLSVAQITLSI-NH2
	1012	Ac-NITLQAKIKQFINMWQEVGKAMYA-NH2
	1013	Ac-LENERTLDFHDSNVKNLYDKVRLQLRDN-NH2
10	1014	Ac-LENERTLDFHDSNVKNLYDKVRLQLRDNVKELGNG-NH2
	1015	Ac-TLDFHDSNVKNLYDKVRLQLRDNVKELGNGAFEF-NH2
	1016	Ac-IDISIELNKAQSDLEESKEWIKKSNQKLD SIGNWH-NH2
	1021	Biotinyl-SISQVNEEINQALAYIRKADELL-NH2
	1022	Biotinyl-SISQVNEEINQSLAYIRKSDELL-NH2
	1023	Ac-SISQVNEEINQSLAYIRKSDELL-NH2
	1024	Ac-IDISIELNKAQSDLEESKEWIEKSNQELDSIGNWE-NH2
	1025	Ac-IDISIELNKAQSDLEESKEWIKKSNQELDSIGNWH-NH2
15	1026	Ac-IDISIELNKAQSDLEEAKWIDDANQKLD SIGNWH-NH2
	1027	Ac-IDISIELNKAQSDLEESKEWIKKANQKLD SIGNWH-NH2
	1028	Ac-IDISIELNKAQSDLEEAKWIKKSNQKLD SIGNWH-NH2
	1029	Biotinyl-NSVALDPIDISIELNKAQSDLEESKEWIKKSNQKL-NH2
	1030	Biotinyl-ALDPIDISIELNKAQSDLEESKEWIKKSNQKLD SI-NH2
	1031	desAminoTyrosine-NSVALDPIDISIELNKAQSDLEESKEWIKKSNQKL-NH2
	1032	desAminoTyrosine-ALDPIDISIELNKAQSDLEESKEWIKKSNQKLD SI-NH2
	1033	Ac-YDASISQVNEEINQALAFIRKADEL-NH2
20	1034	Ac-YDASISQVNEEINQSLAYIRKADELL-NH2
	1035	Biotinyl-YDASISQVNEEINQALAYIRKADELL-NH2
	1036	Biotinyl-YDASISQVNEEINQSLAFIRKSDELL-NH2
	1037	Ac-YDASISQVNEEINQSLAFIRKSDELL-NH2
	1038	Ac-WLEWDREINNYTSLIHSLIEESQNQQEKNEQEL-NH2
	1039	Biotinyl-IDISIELNKAQSDLEESKEWIRRSNQKLD SIGNWH-NH2
	1044	Ac-YESTQKAFDGITNKVNSVIEKTNTQFEAVGKEFGNLEKR-NH2
	1045	Biotin-DEYDASISQVNEKINQSLAFIRKSDELL-NH2
25	1046	Ac-MEWDREINNYTSLIHSLIEESQNQQEKNEQEL-NH2
	1047	Ac-WQEWEQKVRYLEANISQSLEQAQIQQEKKNMYEL-NH2
	1048	Ac-WQEWEQKVRYLEANISQSLEQAQIQQEKKNEYEL-NH2
	1049	Ac-WQEWEQKVRYLEANITALLEQAQIQQEKKNEYEL-NH2
	1050	Ac-WQEWEQKVRYLEANITALLEQAQIQQEKKNMYEL-NH2
	1051	Ac-WQEWEQKVRYLEANISQSLEQAQIQQEKKNEYELQKL-NH2
	1052	Ac-WQEWEQKVRYLEANITALLEQAQIQQEKKNEYELQKL-NH2
	1053	Ac-WQEWEQKVRYLEANITALLEQAQIQQEKKNMYELQKL-NH2
	1054	Ac-IDISIELNKAQSDLEESKEWIEKSNQKLD SIGNWH-NH2
30	1055	Ac-EFGNLEKRLNENLNKRVEDGFLDVWVTYNAELLVALENE-NH2
	1056	Ac-EDGFLDVWVTYNAELLVLMENERTLDFHDSNVKNLYDKVRMQL-NH2
	1057	Ac-SISQVNEKINQSLAFIRKSDELL-NH2

T	No.	Sequence
	1058	desaminoTyr-SISQVNEKINQSLAFIRKSDELL-NH2
	1059	Ac-SISQVNEKINQSLAYIRKSDELL-NH2
	1060	Ac-QQLLDVVKRQQEMLRLTVWGTKNLQARVTAIEKYLKDQ-NH2
	1061	YTSLIHSLIEESQNQQEKNEQELLELDKASLWNWFC
	1062	Ac-FDASISQVNEKINQSLAYIRKSDELL-NH2
	1063	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWA
5	1064	Indole-3-acetyl-DEFDASISQVNEKINQSLAFIRKSDELL-NH2
	1065	Indole-3-acetyl-DEFDESISQVNEKINQSLAFIRKSDELL-NH2
	1066	Indole-3-acetyl-DEFDESISQVNEKIEQSLAFIRKSDELL-NH2
	1067	Indole-3-acetyl-DEFDESISQVNEKIEESLAFIRKSDELL-NH2
	1068	Indole-3-acetyl-DEFDESISQVNEKIEESLQFIRKSDELL-NH2
	1069	Indole-3-acetyl-GGGGDEFDASISQVNEKINQSLAFIRKSDELL-NH2
	1070	2-Napthoyl-DEFDASISQVNEKINQSLAFIRKSDELL-NH2
	1071	desNH2Tyr-DEFDASISQVNEKINQSLAFIRKSDELL-NH2
10	1072	biotin-ALDPIDISIELNKAKSDEESKEWIRRSNQKLDSEI-NH2
	1073	Ac-YDASISQVNEKINQALAYIRKADELHNVNAGKST-NH2
	1074	Ac-VYPSDEYDASISQVNEKINQALAYIRKADELHNV-NH2
	1075	Ac-VYPSDEYDASISQVNEKINQSLAYIRKSDELHNV-NH2
	1076	Ac-WGWGYGYG-NH2
	1077	Ac-YGWGWGWGF-NH2
	1078	Ac-WQEWQKVRYLEANITALQEQAQIAEKAAYELQKL-NH2
	1079	Ac-WQEWQKVRYLEAEITALQEQAQIAEKAAYELQKL-NH2
15	1081	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKAS
	1082	Ac-VWPSDEFDASISQVNEKINQSLAFIRKSDELHNV-NH2
	1083	Ac-SKNISEQIDQIKKDEQKEGTGWGLGGKWWTSDWGV-NH2
	1084	Ac-LSKNISEQIDQIKKDEQKEGTGWGLGGKWWTSDWG-NH2
	1085	Ac-DLSKNISEQIDQIKKDEQKEGTGWGLGGKWWTSDW-NH2
	1086	Ac-EDLSKNISEQIDQIKKDEQKEGTGWGLGGKWWTSD-NH2
	1087	Ac-IEDLSKNISEQIDQIKKDEQKEGTGWGLGGKWWTS-NH2
	1088	Ac-GIEDLSKNISEQIDQIKKDEQKEGTGWGLGGKWWT-NH2
20	1089	Ac-IGIEDLSKNISEQIDQIKKDEQKEGTGWGLGGKWW-NH2
	1090	2-Napthoyl--PSDEFDASISQVNEKINQSLAFIRKSDELHNV-NH2
	1091	Ac-VYPSDEYDASISQVNEKINQALAYIRKADELLENV-NH2
	1092	Ac-VYPSDEFDASISQVNEKINQALAFIRKADELLENV-NH2
	1093	Ac-VYPSDEYDASISQVNEKINQALAYIREADELLENV-NH2
	1094	Biotinyl-YDASISQVNEKINQSLAFIREDELLENV-NH2
	1095	Ac-AIGIEDLSKNISEQIDQIKKDEQKEGTGWGLGGKW-NH2
	1096	Ac-AAIGIEDLSKNISEQIDQIKKDEQKEGTGWGLGGK-NH2
25	1097	Ac-DAAIGIEDLSKNISEQIDQIKKDEQKEGTGWGLGG-NH2
	1098	Ac-PDAAIGIEDLSKNISEQIDQIKKDEQKEGTGWGLG-NH2
	1099	Ac-NITDKIDQIIHDFVDKTLPDQGDNDNWWTGWRQWI-NH2
	1100	Ac-KNITDKIDQIIHDFVDKTLPDQGDNDNWWTGWRQW-NH2
	1101	Ac-TKNITDKIDQIIHDFVDKTLPDQGDNDNWWTGWRQ-NH2
	1102	Ac-WTKNITDKIDQIIHDFVDKTLPDQGDNDNWWTGWR-NH2
	1103	Ac-DWTKNITDKIDQIIHDFVDKTLPDQGDNDNWWTGW-NH2
	1104	Ac-HDWTNITDKIDQIIHDFVDKTLPDQGDNDNWWTG-NH2
	1105	Ac-PHDWTNITDKIDQIIHDFVDKTLPDQGDNDNWWT-NH2
30	1106	Ac-EPHDWTNITDKIDQIIHDFVDKTLPDQGDNDNWW-NH2
	1107	Ac-IEPHDWTNITDKIDQIIHDFVDKTLPDQGDNDNW-NH2
	1108	Ac-AIEPHDWTNITDKIDQIIHDFVDKTLPDQGDNDN-NH2

T No.	Sequence
1109	Ac-AAIEPHDWTKNITDKIDQIIHDFVDKTLPDQGDND-NH2
1110	Ac-DAAIEPHDWTKNITDKIDQIIHDFVDKTLPDQGDND-NH2
1111	Ac-LSPTVWLSVIWMMWYWGPSLYSILSPFLPLLPIFF-NH2
1112	Ac-GLSPTVWLSVIWMMWYWGPSLYSILSPFLPLLPIF-NH2
1113	Ac-VGLSPTVWLSVIWMMWYWGPSLYSILSPFLPLLPI-NH2
1114	Ac-FVGLSPTVWLSVIWMMWYWGPSLYSILSPFLPLL-NH2
5 1115	Ac-WFVGLSPTVWLSVIWMMWYWGPSLYSILSPFLPLL-NH2
1116	Ac-QWFVFLSPTVWLSVIWMMWYWGPSLYSILSPFLPL-NH2
1117	Ac-VQWFVGLSPTVWLSVIWMMWYWGPSLYSILSPFLP-NH2
1118	Ac-FVQWFVGLSPTVWLSVIWMMWYWGPSLYSILSPFL-NH2
1119	Ac-PFVQWFVGLSPTVWLSVIWMMWYWGPSLYSILSPF-NH2
1120	Ac-VPFVQWFVGLSPTVWLSVIWMMWYWGPSLYSILSP-NH2
1121	Ac-LVPFVQWFVGLSPTVWLSVIWMMWYWGPSLYSILS-NH2
1122	H-NHTTWMEWDREINNYTSLIHSLIEESQNQQEKNEQELLELDKW-OH
10 1123	H-QARQLSGIVQQNNLLRAIEAQHLLQLTVWGKQLQARILAVERYLKDQ-OH
1124	Ac-VYPSDEFDASISQVNEKINQSLAFIREADELLENV-NH2
1125	Ac-VFPSDEFDASISQVNEKINQSLAYIREADELLENV-NH2
1126	Ac-DEFDASISQVNEKINQSLAYIREADELL-NH2
1127	Ac-NEQELLELDKWASLWNWFGGGGDEFDASISQVNEKINQSLAFIRKSDELL-NH2
1128	Ac-LELDKWASLWNWFGGGGDEFDASISQVNEKINQSLAFIRKSDELL-NH2
1129	Naphthoyl-EGEGEGEGDEFDASISQVNEKINQSLAFIRKSDELL-NH2
1130	Ac-ASRKCRAKFKQLLQHYREVAAAKSENDRLRLLLKQMCPSLDV-NH2
15 1131	Naphthoyl-GDEEDASISQVNEKINQSLAFIRKSDELL-NH2
1132	Naphthoyl-GDEEDASESQVNEKINQSLAFIRKSDELL-NH2
1133	Naphthoyl-GDEEDASESQNEKINQSLAFIRKSDELL-NH2
1134	Naphthoyl-GDEEDASESQNEKQNSLAFIRKSDELL-NH2
1135	Naphthoyl-GDEEDASESQNEKQNSEAFIRKSDELL-NH2
1136	Ac-WGDEFDESISQVNEKIEESLAFIRKSDELL-NH2
1137	Ac-YTSLGGDEFDESISQVNEKIEESLAFIRKSDELLGGWNWF-NH2
1138	Ac-YTSLIHSLGGDEFDESISQVNEKIEESLAFIRKSDELLGGWASLWNWF-NH
20 1139	2-Naphthoyl-GDEFDESISQVNEKIEESLAFIRKSDELL-NH2
1140	2-Naphthoyl-GDEEDESISQVNEKIEESLAFIRKSDELL-NH2
1141	2-Naphthoyl-GDEEDESISQVQEKIEESLAFIRKSDELL-NH2
1142	2-Naphthoyl-GDEEDESISQVQEKIEESLLFIRKSDELL-NH2
1143	Biotin-GDEYDESISQVNEKIEESLAFIRKSDELL-NH2
1144	2-Naphthoyl-GDEYDESISQVNEKIEESLAFIRKSDELL-NH2
1145	Ac-YTSLIHSLIDEQEKIEELAFIRKSDELLELDKWNWF-NH2
1146	VYPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
25 1147	Ac-NNLLRAIEAQHLLQLTVWGSKQLQARILAVERYLKDQ-NH2
1148	GGGVYPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
1149	Ac-NNLLRAIEAQHLLQLTVWGEKQLQARILAVERYLKDQ-NH2
1150	Ac-PTRVNYILIIIGVLVLAbuEVTGVRADVHLL-NH2
1151	Ac-PTRVNYILIIIGVLVLAbuEVTGVRADVHLLLEQPGNLW-NH2
1152	Ac-PEKTPLLPTRVNYILIIIGVLVLAbuEVTGVRADVHLL-NH2
1153	AhaGGGVYPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
1155	Ac-YTSLIHSLGGDEFDESISQVNEKIEESLAFIRKSDELL-NH2
1156	Ac-YTSLGGDEFDESISQVNEKIEESLAFIRKSDELL-NH2
30 1157	Ac-DEFDESISQVNEKIEESLAFIRKSDELLGGWASLWNWF-NH2
1158	Ac-DEFDESISQVNEKIEESLAFIRKSDELLGGWNWF-NH2
1159	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKASLWNWF-NH2

T	No.	Sequence
	1160	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKSLWNWF-NH2
	1161	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKLWNWF-NH2
	1162	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWNWF-NH2
	1163	Ac-MTWMEWDREINNYTSLIHSLIEESQNQQEKNEQELLELDKASLWNWF-NH2
	1164	Ac-MTWMEWDREINNYTSLIHSLIEESQNQQEKNEQELLELDKSLWNWF-NH2
5	1165	Ac-MTWMEWDREINNYTSLIHSLIEESQNQQEKNEQELLELDKLWNWF-NH2
	1166	Ac-MTWMEWDREINNYTSLIHSLIEESQNQQEKNEQELLELDKWNWF-NH2
	1167	Ac-MTWMEWDREINNYTSLIHSLIEESQNQQEKNEQELLELDKASLWN-NH2
	1168	Ac-MTWMEWDREINNYTSLIHSLIEESQNQQEKNEQELLELDKASL-NH2
	1169	(Pyr)HWSY(2-naphthyl-D-Ala)LRPG-NH2
	1170	Ac-WNWFDEFDESISQVNEKIEESLAFIRKSDELLWNWF-NH2
	1171	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKYASLYNYF-NH2
	1172	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKYAYLYNYF-NH2
10	1173	2-Naphthoyl-AcaAcaAcaGDEFDESISQVNEKIEESLAFIRKSDELLAcaAcaAcaW-NH2
	1174	2-Naphthoyl-AcaAcaAcaGDEFDESISQVNEKIEESLAFIRKSDELLGacaAcaAcaW-NH2
	1175	2-Naphthoyl-GDEFDESISQVNEKIEESLAFIRESDELL-NH2
	1176	2-Naphthoyl-GDEFDESISQVNEKIEESLAFIEESDELL-NH2
	1177	Ac-WQEWQKVNYLEANITALLEQAQIQQEKNEYELQKL-NH2
	1178	Ac-WQEWQKVDYLEANITALLEQAQIQQEKNEYELQKL-NH2
	1179	Ac-WQEWQKVRWLEANITALLEQAQIQQEKNEYELQKL-NH2
	1180	Ac-WQEWQKVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
	1181	Ac-WQEWQKVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
15	1182	Ac-WQEWQKVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
	1183	Ac-WQEWQKVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
	1184	Ac-WQEWQKVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
	1185	Ac-WQEWQKVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
	1186	Ac-WQEWQKVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
	1187	Ac-WQEWQKVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
	1188	Ac-VNalPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
	1189	Ac-VNalPSDENalDASISQVNEEINQALAYIRKADELLENV-NH2
20	1190	Ac-VNalPSDEYDASISQVNEEINQALANalIRKADELLENV-NH2
	1191	Ac-VYPSDEFDASISQVNEKINQSLAFIREADELLFNFF-NH2
	1192	Ac-VYPSDEFDASISQVNEEINQALAYIRKADELLENV-NH2
	1193	Ac-YTSLITALLEQAQIQQEKNEYELQKLDKASLWNWF-NH2
	1194	Ac-YTSLITALLEQAQIQQEKNEYELQKLDKASLWFW-NH2
	1195	Ac-YTSLITALLEQAQIQQEKNEYELQKLDKASLWFW-NH2
	1196	Ac-YTSLITALLEQAQIQQEKNEYELQKLDKASLWFW-NH2
	1197	Ac-YTSLITALLEQAQIQQEKNEYELQKLDKASLWFW-NH2
25	1198	Naphthoyl-Aua-Aua-Aua-TALLEQAQIQQEKNEYELQKLAua-Aua-Aua-W-NH2
	1199	Ac-WAWEQKVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
	1200	Ac-WQEAQKVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
	1201	Ac-WQEAQKVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
	1202	Ac-WQEAQKVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
	1203	Ac-WQEAQKVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
	1204	Ac-WQEAQKVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
	1205	Ac-WQEAQKVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
	1206	Ac-WQEAQKVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
30	1207	Ac-WQEAQKVRYLEANITALLEQAQIQQEKNEYELQKLGAGGASLWNF-NH2
	1208	2-Naphthoyl-GDEFDASISQVNEKINQSLAFIRKSDEL-NH2
	1209	2-Naphthoyl-GDEFDASISQVNEKINQSLAFIRKSDEL-NH2

T	No.	Sequence
	1210	2-Naphthoyl-GDEFDASISQVNEKTNQSLAFTRKSDELT-NH2
	1211	2-Naphthoyl-GDEFDASISQVNEKTNQSLAFTRKSDELT-NH2
	1212	2-Naphthoyl-GDEFDASTSQVNEKTNQSLAFTRKSDELT-NH2
	1213	2-Naphthoyl-GDEYDASTSQVNEKTNQSLAFTRKSDELT-NH2
	1214	2-Naphthoyl-GDEFDEEISQVNEKIEESLAFIRKSDELL-NH2
5	1215	2-Naphthoyl-GDEFDASISQVNEKINQSLAFIRKSDELA-NH2
	1216	2-Naphthoyl-GDEFDASASQANEKANQSLAFARKSDELA-NH2
	1217	2-Naphthoyl-GDEFDEISQVNEKIEESLAFTRKSDELL-NH2
	1218	2-Naphthoyl-GDEFDEISQVNEKTEESLAFIRKSDELL-NH2
	1219	2-Naphthoyl-GDEFDEISQVNEKIEESLAFIRKSDELL-NH2
	1220	2-Naphthoyl-GDEFDESTSQVNEKIEESLAFIRKSDELL-NH2
	1221	Ac-WNWFDEFDESTSQVNEKIEESLAFIRKSDELLWNWF-NH2
	1222	Ac-WNWFDEFDESTSQVNEKIEESLAFIRKSDELLWNWF-NH2
	1223	Ac-WNWFDEFDESTSQVNEKIEESLAFIRKSDELLWNWF-NH2
10	1224	Ac-LQAGFFLLTRILTIPQSLDSWWTSLNFLGGTTVAL-NH2
	1225	Ac-YTNLIYTLLEESQNQQEKNEQELLELDKWLWWSWF-NH2
	1226	Ac-WQEWQKVRYLEANITALLEQAQIQQEKNEYELQKLDKWLWWSWF-NH2
	1227	Ac-NNMTWQEWQKVRYLEANITALLEQAQIQQEKNEYELQKLDKWLWWSWF-NH2
	1230	Ac-WNWFIEESDELLWNWF-NH2
	1231	2-Naphthoyl-GFIEESDELLW-NH2
	1232	Ac-WFIEESDELLW-NH2
	1233	2-Naphthoyl-GFNFFIEESDELLFNFF-NH2
15	1234	2-Naphthoyl-GESDELW-NH2
	1235	Ac-WNWFDEFDEISQVQEEIEESLAFIEESDELLGGWNWF-NH2
	1236	Ac-WNWFIEESLIEESQNQQEKNEQELLELDKWLWWSWF-NH2
	1237	Ac-YTSLITALLEQAQIQQEEENYELQALDEWASLWWSWF-NH2
	1238	Ac-YTSLIHSLGGDEFDEISQVNEEIEESLAFIEESDELLGGWASLWWSWF-NH2
	1239	2-Naphthoyl-GDEFDEISQVQEEIEESLAFIEESDELL-NH2
	1240	H-QARQLLSIMQQNNLLRAIEAQHLLQLTVWGKQLQARILAVERYLKDQ-OH
	1241	Ac-CPKYVKQNTLKLATGMRNVPEKQTR-NH2
20	1242	Ac-GLFGAIAGFIENGWEGMIDGWYGRHQNSC-NH2
	1243	Ac-LNFLGGT-NH2
	1244	Ac-LDSWWTSLNFLGGT-NH2
	1245	Ac-ILTIPQSLDSWWTSLNFLGGT-NH2
	1246	Ac-GFFLLTRILTIPQSLDSWWTSLNFLGGT-NH2
	1247	Ac-WQEWQKITALLEQAQIQQEKNEYELQKLDKWLWWSWF-NH2
	1248	Ac-WNWFITALLEQAQIQQEKNEYELQKLDKWLWWSWF-NH2
	1249	Ac-WQEWQKITALLEQAQIQQEKNEYELQKLDKWLWWSWF-NH2
25	1250	Ac-WQEWQKVRYLEANITALLEQAQIQQEKIEYELQKL-NH2
	1251	Ac-WQEWQKVRYLEAQITALLEQAQIQQEKIEYELQKL-NH2
	1252	Ac-KENKANGTDAKVKLKQELDKYKNAVTELQLLMQS-NH2
	1253	Ac-NIKENKANGTDAKVKLKQELDKYKNAVTELQLLM-NH2
	1254	(FS) -YTSLIHSLIEESQNQQEKNEQELLELDKWLWWSWF-NH2
	1255	2-Naphthoyl-GWNWFAcADEFDEISQVQEEIEESLAFIEESDELLAcAaWNWF-NH2
	1256	Ac-WNWFDEFDEISQVNEKIEESLAFIEESDELLGGWNWF-NH2
	1257	Ac-WNWFDEFDEISQVNEKIEESLAFIRKSDELLGGWNWF-NH2
	1258	Ac-WNWF-Aca-DEFDEISQVNEKIEESLAFIRKSDELL-Aca-WNWF-NH2
30	1259	Ac-WNWF-Aca-DEFDEISQVNEKIEESLAFIEESDELL-Aca-WNWF-NH2
	1260	Ac-EESQNQQEKNEQELLELDKWA-NH2
	1261	EESQNQQEKNEQELLELDKWA

T	No.	Sequence
	1262	Ac-CGTTDRSGAPTYSWGANDTDVFLNNTRPPLGNWFG-NH2
	1263	Ac-GVEHRLEAACNWTRGERADLEDNRSELS-NH2
	1264	Ac-CVREGNASRAWVAVTPTVATRDGKLPT-NH2
	1265	Ac-CFSPRHHWTTQDANASIYPG-NH2
	1266	Ac-LQHYREVAAAKSSENDRLRLLLKQMCPSLDVDS-NH2
5	1267	Ac-WQEWDRISNYTSLITALLEQAQIQQEKNEYELQKLDWASLWEWF-NH2
	1268	Ac-CWQEWDRISNYTSLITALLEQAQIQQEKNEYELQKLDWASLWEWFC-NH2
	1269	Ac-WQEWDRISNYTSLITALLEQAQIQQEKNEYELQKLDWEWF-NH2
	1270	Ac-CWQEWDRISNYTSLITALLEQAQIQQEKNEYELQKLDWEWFC-NH2
	1271	Ac-GQNSQSPTSNSHPTSAPPTAPGYRWA-NH2
	1272	Ac-PGSSTTSTGPARTALTTAQGTSLYPSA-NH2
	1273	Ac-PGSSTTSTGPARTALTTAQGTSLYPSAAATKPSDGNATA-NH2
	1275	Ac-WQEWDRITALLEQAQIQQEKNEYELQKLDKASLWNWF-NH2
	1276	Ac-WQEWDRITALLEQAQIQQEKNEYELQKLDWASLWEWF-NH2
10	1277	Ac-WQEWDRITALLEQAQIQQEKNEYELQKLDWEWF-NH2
	1278	Ac-WQEWDRITALLEQAQIQQEKNEYELQKLDWEWF-NH2
	1279	Ac-WQEWREITALLEQAQIQQEKNEYELQKLIWEWF-NH2
	1280	Ac-WQEWREITALLEQAQIQQEKIEYELQKLDWEWF-NH2
	1281	Ac-WQEWREITALLEQAQIQQEKNEYELQKLDWEWF-NH2
	1282	Ac-WQEWREITALLEQAQIQQEKIEYELQKLIWEWF-NH2
	1283	Ac-WQEWREITALLEQAQIQQEKIEYELQKLDWEWF-NH2
	1284	Ac-WQEWREITALLEQAQIQQEKIEYELQKLIWEWF-NH2
15	1285	Ac-WQEWDRIDEYDASISQVNEKINQALAYIREADELWEWF-NH2
	1286	Ac-WQEWREIDEYDASISQVNEKINQALAYIREADELWEWF-NH2
	1287	Ac-WQEWREIDEYDASISQVNEKINQALAYIREADELWEWF-NH2
	1288	Ac-WQEWDRIDEYDASISQVNEEINQALAYIREADELWEWF-NH2
	1289	Ac-WQEWREIDEYDASISQVNEEINQALAYIREADELWEWF-NH2
	1290	Ac-WQEWREIDEYDASISQVNEEINQALAYIREADELWEWF-NH2
	1291	Ac-WQEWREIDEYDASISQVNEEINQALAYIREADELWEWF-NH2
	1292	Ac-WQEWREIDEYDASISQVNEEINQALAYIREADELWEWF-NH2
20	1293	Ac-WQEWREIDEYDASISQVNEEINQALAYIREADELWEWF-NH2
	1294	Ac-WQEWREIDEYDASISQVNEEINQALAYIREADELWEWF-NH2
	1295	Ac-WQEWREIDEYDASISQVNEEINQALAYIREADELWEWF-NH2
	1298	-VYPSDEYDASISQVNEEINQALAYIRKADLELNV-NH2
	1299	Ac-WVYPSDEYDASISQVNEEINQALAYIRKADLELNVWNWF-NH2
	1300	YTSLIHSLIEESQSQQEKNEQELLELDKASLWNWF-NH2
	1301	Ac-WQEWREIDEYDASISQVNEKINQALAYIREADELWAWF-NH2
	1302	Ac-WQAWREIDEYDASISQVNEKINQALAYIREADELWAWF-NH2
25	1303	Ac-WQAWREIDEYDASISQVNEKINQALAYIREADELWEWF-NH2
	1304	Biotin-YDPLVFPSDEFDASISQVNEKINQSLAFIRKSDDEL-NH2
	1305	Biotin-YDPLVFPSDEFDASISQVNEKINQSLAF-NH2
	1306	Biotin-QVNEKINQSLAFIRKSDLELHNVNAGKST-NH2
	1307	Ac-WMEWDR-E-NH2
	1308	Ac-WQEWREIDEYDASISQVNEEINQALAYIRKADLELNV-NH2
	1309	Ac-WQEWREIDEYDASISQVNEEINQALAYIRKADLELNV-NH2
	1310	Ac-WQEWREIDEYDASISQVNEEINQALAYIRKADLELNV-NH2
30	1311	Ac-WQEWREIDEYDASISQVNEEINQALAYIRKADLELNV-NH2
	1312	Ac-WQEWREIDEYDASISQVNEEINQALAYIRKADLELNV-NH2
	1313	Ac-WQEWREIDEYDASISQVNEEINQALAYIRKADLELNV-NH2
	1314	Ac-WQEWREIDEYDASISQVNEEINQALAYIRKADLELNV-NH2

T	No.	Sequence
	1315	Ac-FNLSDHSESIQKKFQLMKKHVNKIGVSDPIGWSLR-NH2
	1316	Ac-DHSESIQKKFQLMKKHVNKIGVSDPIGWSLRGIF-NH2
	1317	Ac-WSVKQANLTTSLLDGDDVTSIRHAVLQNR-NH2
	1318	Biotin-WMEWDREI-NH2
	1319	Biotin-NNMTWMEWDREINNYTSL-NH2
5	1320	Ac-GAASLTTLTVQARQLLSGIVQQQNNLLRAIEAQQHLL-NH2
	1321	Ac-ASLTTLTVQARQLLSGIVQQQNNLLRAIEAQQHLLQL-NH2
	1322	Ac-VSVGNTLYYVKNQEGKSLYVKGEPIINFYDPLVF-NH2
	1323	Ac-QHWSYGLRPG-NH2
	1324	Ac-WQEWQKIQHWSYGLRPGWASLWEWF-NH2
	1325	Ac-WQEWQKIQHWSYGLRPGWEWF-NH2
	1326	Ac-WNWFQHWSYGLRPGWNWF-NH2
	1327	Ac-FNFFQHWSYGLRPGFNFF-NH2
	1328	Ac-GAGAQHWSYGLRPGAGAG-NH2
10	1329	PLLVLQAGFFLLTRILTIPQSLDSWWTSLNFLGGT
	1330	Ac-WQEWQKITALLEQAQIQQEKIEYELQKLAKWASLWEWF-NH2
	1331	Ac-WQEWQKITALLEQAQIQQEKIEYELQKLAEWASLWEWF-NH2
	1332	Ac-WQEWQKITALLEQAQIQQEKAEYELQKLAEWASLWEWF-NH2
	1333	Ac-WQEWQKITALLEQAQIQQEKAEYELQKLAEWASLWAWF-NH2
	1334	Ac-WQEWQKITALLEQAQIQQEKAEYELQKLAKWASLWAWF-NH2
	1335	Ac-TNKAVVSLSNGVSVLTSKVLDLKNYIDKQLLPVNVK-NH2
	1336	Ac-KAVVSLSNGVSVLTSKVLDLKNYIDKQLLPVNVKQS-NH2
15	1337	Ac-WQEWQKITALLEQAQIQQEKNEYELQKLIWEWF-NH2
	1338	Ac-WQEWQKITALLEQAQIQQEKNEYELQKLIWEWF-NH2
	1339	Ac-WQEWQKITALLEQAQIQQEKIEYELQKLDKWEWF-NH2
	1340	Ac-YDPLVFPSEFDASISQVNEKINQSLAF-NH2
	1341	Fluor--VYPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
	1342	Fluor-YTSLIHSLEESQNQQEKNEQELLELDKWASLWNWF-NH2
	1344	Ac-SGIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARIL-NH2
	1345	Ac-QQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
20	1346	Ac-SGIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
	1347	Ac-WQEWQKITALLEQAQIQQEKNEYELQKLAEWASLWAWF-NH2
	1348	Ac-WQEWQKITALLEQAQIQQEKNEYELQKLAEWASLWAW-NH2
	1349	Ac-WQEWQKITALLEQAQIQQEKAEYELQKLAEWASLWAW-NH2
	1350	Ac-WQEWQKITALLEQAQIQQEKNEYELQKLAEWAGLWAWF-NH2
	1351	Ac-WQEWQKITALLEQAQIQQEKNEYELQKLAEWAGLWAW-NH2
	1352	Ac-WQEWQKITALLEQAQIQQEKAEYELQKLAEWAGLWAW-NH2
	1353	Ac-WQEWQKITALLEQAQIQQEKNEYELQKLDKWAGLWEWF-NH2
25	1354	Ac-WQEWQHWSYGLRPGWEWF-NH2
	1355	Ac-WQAWQHWSYGLRPGWAWF-NH2
	1356	Biotinyl-WQEWQKITALLEQAQIQQEKNEYELQKLDKWASLWEWF-NH2
	1357	WQEWQKITALLEQAQIQQEKNEYELQKLDKWASLWEWF
	1358	WQEWQKITALLEQAQIQQEKIEYELQKLIWEWF
	1361	Ac-AGSTMGARSMTTLTVQARQLLSGIVQQQNNLLRAIEAQQ-NH2
	1362	Ac-AGSAMGAASLTLSAQSRRTLLAGIVQQQQQLLDVVKRQQ-NH2
	1363	Ac-AGSAMGAASTALTAQSRRTLLAGIVQQQQQLLDVVKRQQ-NH2
	1364	Ac-ALTAQSRRTLLAGIVQQQQQLLDVVKRQQELLRLTVWGT-NH2
30	1365	Ac-TLSAQSRRTLLAGIVQQQQQLLDVVKRQQEMRLRLTVWGT-NH2
	1366	Ac-TTLTVQARQLLSGIVQQQNNLLRAIEAQQHLLQLTVWGI-NH2
	1367	Ac-WQAWIEYEAEELSQVKEKIEQSLAYIREADELWAWF-NH2

T	No.	Sequence
	1368	AC-WQAWIEYEASLSQAKEKIEESKAYIREADELWAWF-NH2
	1369	AC-WQAWIEYERLLVQAKLKIAIAKLYIAKELLEWAWF-NH2
	1370	AC-WQAWIEYERLLVQVKLKIAIALLYIAKELLEWAWF-NH2
	1371	AC-WQAWIELERLLVQVKLKIAIAKLEIAKELLEWAWF-NH2
	1372	AC-GEWTYDDATKTFTVTEGGH-NH2
5	1373	AC-WQEWQKIGEWTYDDATKTFTVTEGGHWASLWEWF-NH2
	1374	AC-GEWTYDDATKTFTVTE-NH2
	1375	AC-WQEWQKIGEWTYDDATKTFTVTEWASLWEWF-NH2
	1376	AC-MHRFDYRT-NH2
	1377	AC-WQEWQKIMHRFDYRTWASLWEWF-NH2
	1378	AC-MHRFNWSTGGG-NH2
	1379	AC-WQEWQKIMHRFNWSTGGGWASLWEWF-NH2
	1380	AC-MHRFNWST-NH2
	1381	AC-WQEWQKIMHRFNWSTWASLWEWF-NH2
10	1382	AC-LLVPLARIMTMSSVHGGG-NH2
	1383	AC-WQEWQKILLVPLARIMTMSSVHGGGWASLWEWF-NH2
	1384	AC-LLVPLARIMTMSSVH-NH2
	1385	AC-WQEWQKILLVPLARIMTMSSVHWASLWEWF-NH2
	1386	TALLEQAQIQQEKNEYELQKLDK
	1387	AC-TALLEQAQIQQEKNEYELQKLDK-NH2
	1388	AC-TALLEQAQIQQEKIEYELQKLE-NH2
	1389	TALLEQAQIQQEKIEYELQKLE
15	1390	AC-QARQLLSGIVQQQNNLLRAIEAQHLLQLTVWGIKQLQARILAVERY-NH2
	1391	Rhod-QARQLLSGIVQQQNNLLRAIEAQHLLQLTVWGIKQLQARILAVERY-NH2
	1392	AC-GAASLTLSAQSRLLAGIVQQQQLLDVVKRQQEML-NH2
	1393	AC-GSAMGAASLTLSAQSRLLAGIVQQQQLLDVVKRQQEML-NH2
	1394	AC-PALSTGLIHLHQNIVDVQFLFGVGSSIASWAIKWEY-NH2
	1395	AC-PALSTGLIHLHQNIVDVQFLYGVGSSIASWAIK-NH2
	1396	AC-LSTTQVQLPUSFTTLPALSTGLIHLHQNIVDVQY-NH2
	1397	AC-FRKFPFATFSRUGSGPRITPRUMVDFPFLWHY-NH2
20	1398	AC-DFFPRLWHFPUTINYTIFKVRLFVGGVEHRLEAAUNWTR-NH2
	1399	AC-YVGGVEHRLEAAUNWTRGERUDLEDRDRSELSPL-NH2
	1400	MVYPSDEYDASISQVNEEQALAYIRKADELLENV
	1402	AC-GPLLVLQAGFFLLTRILTIPQSLDSWWTSLNFLGG-NH2
	1403	AC-LGPLLVLQAGFFLLTRILTIPQSLDSWWTSLNFLG-NH2
	1404	AC-FLGPLLVLQAGFFLLTRILTIPQSLDSWWTSLNFL-NH2
	1405	AC-YTNTIYTLLEESQNQQEKNEQELLELDKASLWNWF-NH2
	1406	YTNTIYTLLEESQNQQEKNEQELLELDKASLWNWF
25	1407	AC-YTGIIYNLLEESQNQQEKNEQELLELDKASLWNWF-NH2
	1408	YTGIIYNLLEESQNQQEKNEQELLELDKASLWNWF
	1409	AC-YTSLIYSLLEKSQIQQEKNEQELLELDKASLWNWF-NH2
	1410	YTSLIYSLLEKSQIQQEKNEQELLELDKASLWNWF
	1411	AC-EKSQIQQEKNEQELLELDKWA-NH2
	1412	EKSQIQQEKNEQELLELDKWA
	1413	AC-EQAQIQQEKNEYELQKLDKWA-NH2
	1414	AC-YTSLIGSLIEESQIQQERNEQELLELDKASLWEWF-NH2
	1415	AC-YTXLIHSLIXESQNQQXKNEQELKELDKASLWNWF-NH2
30	1416	AC-YTXLIHSLIYESQNQQXKNEQELKELD-NH2
	1417	AC-YTSLIHSLEESQNQQEKNEQELLELD-NH2
	1418	AC-WQEQEXKITALLXQAQIQQXKNEYELKXKLDKASLWEWF-NH2

T	No.	Sequence
	1419	Ac-XKITALLXQAQIQQXKNEYELXKLDKWASLWEWF-NH2
	1420	Ac-WQEWXKITALLXQAQIQQXKNEYELXKLD-NH2
	1421	Ac-WEQKITALLEQAQIQQEKNEYELQKLD-NH2
	1422	Ac-WEXKITALLXQAQIQQXKNEYELXKLD-NH2
	1423	Ac-XKITALLXQAQIQQXKNEYELXKLD-NH2
5	1425	Ac-QKITALLEQAQIQQEKNEYELQKLD-NH2
	1426	Ac-QKITALLEQAQIQQEKNEYELQKLDKWASLWEWF-NH2
	1427	Ac-WQEWQKITALLEQAQIQQEKNEYELQKLD-NH2
	1428	Ac-VYPSDEYDASISQVNEEINQALAYIRKADELLEN-OH
	1429	Ac-VYPSDEYDASISQVNEEINQALAYIRKADELLE-OH
	1430	Ac-VYPSDEYDASISQVNEEINQALAYIRKADELL-OH
	1431	Ac-VYPSDEYDASISQVNEEINQALAYIRKADEL-OH
	1432	YPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
	1433	PSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
10	1434	SDEYDASISQVNEEINQALAYIRKADELLENV-NH2
	1435	DEYDASISQVNEEINQALAYIRKADELLENV-NH2
	1436	Ac-VYPSDEYDASISQVDEEINQALAYIRKADELLENV-NH2
	1437	Ac-VYPSDEYDASISQVNEEIDQALAYIRKADELLENV-NH2
	1438	Ac-VYPSDEYDASISQVNEEINQALAYIRKADELLEDV-NH2
	1439	Ac-VYPSDEYDASISQVDEEIDQALAYIRKADELLENV-NH2
	1440	Ac-LLSTNKAVVSLSGVSVLTISKVLDLKNYIDKQLLP-NH2
	1441	Ac-LSTNKAVVSLSGVSVLTISKVLDLKNYIDKQLLP-I-NH2
15	1442	Ac-STNKAVVSLSGVSVGTISKVLDLKNYIDKQLLP-IV-NH2
	1443	Ac-TNKAVVSLSGVSVLTISKVLDLKNYIDKQLLP-IVN-NH2
	1444	Ac-NKAVVSLSGVSVLTISKVLDLKNYIDKQLLP-IVNK-NH2
	1445	Ac-KAVVSLSGVSVLTISKVLDLKNYIDKQLLP-IVNKQ-NH2
	1446	Ac-AVVSLSGVSVLTISKVLDLKNYIDKQLLP-IVNKQS-NH2
	1447	Ac-VVSLSGVSVLTISKVLDLKNYIDKQLLP-IVNKQSU-NH2
	1448	Ac-VSLSGVSVLTISKVLDLKNYIDKQLLP-IVNKQSUS-NH2
	1449	Ac-SLSNGVSVLTISKVLDLKNYIDKQLLP-IVNKQSUSI-NH2
20	1450	Ac-LSNGVSVLTISKVLDLKNYIDKQLLP-IVNKQSUSIS-NH2
	1451	Ac-SNGVSVLTISKVLDLKNYIDKQLLP-IVNKQSUSISN-NH2
	1452	Ac-NGVSVLTISKVLDLKNYIDKQLLP-IVNKQSUSISNI-NH2
	1453	Ac-GVSVLTISKVLDLKNYIDKQLLP-IVNKQSUSISNIE-NH2
	1454	Ac-VSVLTISKVLDLKNYIDKQLLP-IVNKQSUSISINIET-NH2
	1455	Ac-SVLTISKVLDLKNYIDKQLLP-IVNKQSUSISNIETV-NH2
	1456	Ac-VLTISKVLDLKNYIDKQLLP-IVNKQSUSISNIETVI-NH2
	1457	Ac-LTSKVLDLKNYIDKQLLP-IVNKQSUSISNIETVIE-NH2
25	1458	Ac-TSKVLDLKNYIDKQLLP-IVNKQSUSISNIETVIEF-NH2
	1459	Ac-SKVLDLKNYIDKQLLP-IVNKQSUSISNIETVIEFQ-NH2
	1460	Ac-KVLDLKNYIDKQLLP-IVNKQSUSISNIETVIEFQQ-NH2
	1461	Ac-VLDLKNYIDKQLLP-IVNKQSUSISNIETVIEFQQK-NH2
	1462	Ac-LDLKNYIDKQLLP-IVNKQSUSISNIETVIEFQQKN-NH2
	1463	Ac-DLKNYIDKQLLP-IVNKQSUSISNIETVIEFQQKNN-NH2
	1464	Ac-LKNYIDKQLLP-IVNKQSUSISNIETVIEFQQKNNR-NH2
	1465	Ac-KNYIDKQLLP-IVNKQSUSISNIETVIEFQQKNNRL-NH2
	1466	Ac-NYIDKQLLP-IVNKQSUSISNIETVIEFQQKNNRLL-NH2
30	1467	Ac-YIDKQLLP-IVNKQSUSISNIETVIEFQQKNNRLL-E-NH2
	1468	Ac-IDKQLLP-IVNKQSUSISNIETVIEFQQKNNRLL-EI-NH2
	1469	Ac-DKQLLP-IVNKQSUSISNIETVIEFQQKNNRLL-EIT-NH2

T	No.	Sequence
	1470	Ac-KQLLPVNVKQSUSISNIETVIEFQQKNNRLLLEITR-NH2
	1471	Ac-QLLPVIKQKQSUSISNIETVIEFQQKNNRLLLEITRE-NH2
	1472	Ac-VYPSDEYDASISQVNEEINQALA
	1473	QVNEEINQALAYIRKADELLENV-NH2
	1474	VYPSDEYDASISQVNEEINQALAYIRKADELLENV
5	1475	Ac-DEYDASISQVNEEINQALAYIREADEL-NH2
	1476	Ac-DEYDASISQVNEKINQALAYIREADEL-NH2
	1477	Ac-DDECLNSVKNGTYDFPKFEEESKLNRRNEIKGVKLS-NH2
	1478	Ac-DDE-Abu-LNSVKNGTYDFPKFEEESKLNRRNEIKGVKLS-NH2
	1479	Ac-YHKCDDECLNSVKNGTFDFPKFEEESKLNRRNEIKGVKLSS-NH2
	1480	Ac-YHK-Abu-DDE-Abu-LNSVKNGTFDFPKFEEESKLNRRNEIKGVKLSS-NH2
	1481	Ac-YTSLIHSLIEESQIQEKNQELLELDKWASLWNWF-NH2
	1482	Ac-YTSLIHSLIEESQNQQEKNQELLELDKWASLWNWF-NH2
	1483	Ac-YTSLIHSLIEESQIQEKNQELLELDKWASLWNWF-NH2
10	1484	Ac-YTSLIHSLIEESQIQEKNQELLELDKWASLWNWF-NH2
	1485	Ac-YTSLIHSLIEESQNQQEKNQELLELDKWASLWNWF-NH2
	1486	Ac-YTSLIHSLIEESQNQQEKNQELLELDKWASLWNWF-NH2
	1487	Ac-YTSLIHSLIEESQIQEKNQELLELDKWASLWNWF-NH2
	1488	Ac-YTSLIHSLIEESQNQQEKNQELLELDKWASLWFW-NH2
	1489	Ac-YTSLIHSLIEESQIQEKNQELLELDKWASLWFW-NH2
	1490	Ac-YTSLIHSLIEESQNQQEKNQELLELDKWASLWFW-NH2
	1491	Ac-YTSLIHSLIEESQIQEKNQELLELDKWASLWFW-NH2
15	1492	Ac-YTSLIHSLIEESQIQEKNQELLELDKWASLWFW-NH2
	1493	Ac-YTSLIHSLIEESQNQQEKNQELLELDKWASLWFW-NH2
	1494	Ac-YTSLIHSLIEESQNQQEKNQELLELDKWASLWFW-NH2
	1495	Ac-YTSLIHSLIEESQIQEKNQELLELDKWASLWFW-NH2
	1496	Ac-WQEQEQKITALLEQAQIQEKNQELLELDKQWFW-NH2
	1497	Ac-WQEQEQKITALLEQAQIQEKNQELLELDKQWFW-NH2
	1498	Ac-WQEQEQKITALLEQAQIQEKNQELLELDKQWFW-NH2
	1499	Ac-WQEQEQKITALLEQAQIQEKNQELLELDKQWFW-NH2
20	1500	Ac-WQEQEQKITALLEQAQIQEKNQELLELDKQWFW-NH2
	1501	Ac-WQEQEQKITALLEQAQIQEKNQELLELDKQWFW-NH2
	1502	Ac-WQEQEQKITALLEQAQIQEKNQELLELDKQWFW-NH2
	1503	Ac-WQEQEQKITALLEQAQIQEKNQELLELDKQWFW-NH2
	1504	Ac-WQEQEQKITALLEQAQIQEKNQELLELDKQWFW-NH2
	1505	Ac-WQEQEQKITALLEQAQIQEKNQELLELDKQWFW-NH2
	1506	Ac-WQEQEQKITALLEQAQIQEKNQELLELDKQWFW-NH2
	1507	Ac-WQEQEQKITALLEQAQIQEKNQELLELDKQWFW-NH2
25	1508	Ac-WQEQEQKITALLEQAQIQEKNQELLELDKQWFW-NH2
	1509	Ac-WQEQEQKITALLEQAQIQEKNQELLELDKQWFW-NH2
	1510	Ac-WQEQEQKITALLEQAQIQEKNQELLELDKQWFW-NH2
	1511	Ac-WQEQEQKITALLEQAQIQEKNQELLELDKQWFW-NH2
	1512	Ac-WQEQEQKITALLEQAQIQEKNQELLELDKQWFW-NH2
	1513	Ac-WQEQEQKITALLEQAQIQEKNQELLELDKQWFW-NH2
	1514	Ac-WQEQEQKITALLEQAQIQEKNQELLELDKQWFW-NH2
	1515	Ac-WQEQEQKITALLEQAQIQEKNQELLELDKQWFW-NH2
	1516	Ac-WQEQEQKITALLEQAQIQEKNQELLELDKQWFW-NH2
30	1517	Ac-WQEQEQKITALLEQAQIQEKNQELLELDKQWFW-NH2
	1518	Ac-WQEQEQKITALLEQAQIQEKNQELLELDKQWFW-NH2
	1519	Ac-WQEQEQKITALLEQAQIQEKNQELLELDKQWFW-NH2

T No.	Sequence
1520	PEG-GWQEWQRITALLEQAQIQQERNEYELQRLDEWASLWEWF-NH2
1521	Ac-GWQEWQRITALLEQAQIQQERNEYELQRLDEWASLWEWF-NH2
1522	PEG-YTSLITALLEQAQIQQERNEQELLEDEWASLWEWF-NH2
1523	Ac-YTSLITALLEQAQIQQERNEQELLEDEWASLWEWF-NH2
1526	PEG-GWQEWQRITALLEQAQIQQERNEYELQELDEWASLWEWF-NH2
1527	Ac-GWQEWQRITALLEQAQIQQERNEYELQELDEWASLWEWF-NH2
5 1528	PEG-YTSLIGSLIEESQIQQERNEQELLELDRAWASLWEWF-NH2
1529	PEG-GWQEWQRITALLEQAQIQQERNEYELQRLDRAWASLWEWF-NH2
1530	Ac-GWQEWQRITALLEQAQIQQERNEYELQRLDRAWASLWEWF-NH2
1531	PEG-GWQEWQRITALLEQAQIQQERNEYELQELDRAWASLWEWF-NH2
1532	Ac-GWQEWQRITALLEQAQIQQERNEYELQELDRAWASLWEWF-NH2
1533	PEG-YTSLIGSLIEESQNQQERNEQELLELDRAWASLWNWF-NH2
1534	Ac-YTSLIGSLIEESQNQQERNEQELLELDRAWASLWNWF-NH2
1538	Ac-YTSLIHSLIEESQNQQEK-OH
10 1539	NEQELLELDK
1540	WASLWNWF-NH2
1542	Ac-AAAEQKITALLEQAQIQQEKNEYELQKLDKASLWEWF-NH2
1543	Ac-WQEAQKITALLEQAQIQQEKNEYELQKLDKASLWEWF-NH2
1544	Ac-WQEWQAAAALEQAQIQQEKNEYELQKLDKASLWEWF-NH2
1545	Ac-WQEWQKITAAAEQAQIQQEKNEYELQKLDKASLWEWF-NH2
1546	Ac-WQEWQKITALLAAQAQIQQEKNEYELQKLDKASLWEWF-NH2
1547	Ac-WQEWQKITALLEQAQAAAEKNEYELQKLDKASLWEWF-NH2
15 1548	Ac-WQEWQKITALLEQAQIAAANEYELQKLDKASLWEWF-NH2
1549	Ac-WQEWQKITALLEQAQIQQEKAAAEQKLDKASLWEWF-NH2
1550	Ac-WQEWQKITALLEQAQIQQEKNEYAAAKLDKASLWEWF-NH2
1551	Ac-WQEWQKITALLEQAQIQQEKNEYELQAAAKWASLWEWF-NH2
1552	Ac-WQEWQKITALLEQAQIQQEKNEYELQKLDAAASLWEWF-NH
1553	Ac-WQEWQKITALLEQAQIQQEKNEYELQKLDKWAASAEWF-NH
1554	Ac-WQEWQKITALLEQAQIQQEKNEYELQKLDKASLWAAA-NH
1556	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKASLWNWF-NH2
20 1557	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKASLWNWF-NH2
1558	Ac-ERTLDFHDS-NH2
1559	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKASLWN(W)F-NH2
1563	Ac-YTSLIHSLIEESQN(Q)QEKNEQELLELDKASLWNWF-NH2
1564	Ac-YTSLIHSLIEESQNQQDKASLWNWF-NH2
1566	Ac-FYEIIMDIEQNNVQGKKGIIQQLQKWEDWVGWIGNI-NH2
1567	Ac-INQTIWNHGNITLGEWYNQTKDLQQKFYEIIMDIE-NH2
1568	Ac-WNHGNITLGEWYNQTKDLQQKFYEIIMDIEQNNVQ-NH2
25 1572	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKASLWNWF-NH2
1573	Ac-YTSLIHSLIEESQDQQEKNEQELLELDKASLWNWF-NH2
1574	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKASLWNWF-NH2
1575	c-YTSLIHSLIEESQNQQEKNEQELLELDKASLWNWF-NH2
1576	Ac-YTSLIHSLIEESQNQQEKDEQELLELDKASLWNWF-NH2
1577	Ac-LGEWYNQTKDLQQKFYEIIMDIEQNNVQGKKGIIQQ-NH2
1578	Ac-WYNQTKDLQQKFYEIIMDIEQNNVQGKKGIIQQLQK-NH2
1579	Ac-YTSLIHSLIEESQNQQEKNEEELLELDKASLWNWF-NH2
1580	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKASLWDWF-NH2
30 1586	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKASLWNWX-NH2
1588	Ac-YNQTDLQQKFYEIIMDIEQNNVQGKKGIIQQLQKW-NH2
1598	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKASLWNWF

T	No.	Sequence
	1600	Ac-TLTVQARQLLSGIVQQNNLLRAIEAQQHLLQLTVWGIKQLQAR-NH2
	1603	Ac-LQQKFYEIIMDIEQNNVQGGKGIQQLQKWEDWVGW-NH2
	1627	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	1628	Ac-YTSLIHSLIEESQNQQEKNEQELLEADKWASLWNWF-NH2
	1629	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
5	1630	Ac-YTSLIHSLIEESQNQQEKAEQELLELDKWASLWNWF-NH2
	1631	Ac-YTSLIHSLIEESQNQQEKNAQELLELDKWASLWNWF-NH2
	1632	Ac-YTSLIHSLIEESQNQQEKNEAEELLELDKWASLWNWF-NH2
	1634	Ac-WQEWQKITALLEQAQIQQEKNEQELQKLDKWASLWEWF-NH2
	1635	Ac-WQEWQKITALLEQAQIQQEKAEYELQKLDKWASLWEWF-NH2
	1636	Ac-WQEWQKITALLEQAQIQQEKNAVELQKLDKWASLWEWF-NH2
	1637	Ac-WQEWQKITALLEQAQIQQEKNEAELQKLDKWASLWEWF-NH2
	1644	Ac-EYDLRRWEK-NH2
	1645	Ac-EQELLELDK-NH2
10	1646	Ac-EYELQKLDK-NH2
	1647	Ac-WQEWQKITALLEQAQIQQEKNEQELLELDKWASLWEWF-NH2
	1648	Ac-WQEWQKITALLEQAQIQQEKNEQELLELDKWASLWEWF-NH2
	1649	Ac-WQEWQKITALLEQAQIQQEKNDKWASLWEWF-NH2
	1650	Ac-YTSLIHSLIEESQNQAENEQELLELDKWASLWNWF-NH2
	1651	Ac-YTSLIHSLIEESQNQAENEQELLELDKWASLWNWF-NH2
	1652	Ac-YTSLIHSLIEESQNQAENEQELLELDKWASLWNWF-NH2
	1653	Ac-YTSLIHSLIEESANQEAENEQELLELDKWASLWNWF-NH2
15	1654	Ac-YTSLIHSLIEESQAQQEKNEQELLELDKWASLWNWF-NH2
	1655	Ac-YTSLIHSLIEESQNAQEKNEQELLELDKWASLWNWF-NH2
	1656	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	1657	Ac-YTSLIHSAIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	1658	Ac-VYPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
	1659	Ac-YTSLIHSLAEESQNQQEKNEQELLELDKWASLWNWF-NH2
	1660	Ac-YTSAIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	1661	Ac-YTSLAHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
20	1662	Ac-YTSLIASLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	1663	Ac-ATSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	1664	Ac-YASLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	1665	Ac-YTALIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
	1666	Ac-RIQDLEKYVEDTKIDLWSYNAELLVALENQ-NH2
	1667	Ac-HTIDLTDSMNKLFKTRRQLREN-NH2
	1668	Ac-SEMNKLFKTRRQLREN-NH2
	1669	Ac-VFPSDEADASISQVNEKINQSLAFIRKSDELLHNV-NH2
25	1670	Ac-VFPSDEFAASISQVNEKINQSLAFIRKSDELLHNV-NH2
	1671	Ac-VFPSDEFDASISAVNEKINQSLAFIRKSDELLHNV-NH2
	1672	Ac-VFPSDEFDASISQANEKINQSLAFIRKSDELLHNV-NH2
	1673	Ac-VFPSDEFDASISQVAEKINQSLAFIRKSDELLHNV-NH2
	1674	Ac-WQEWQKITAALEQAQIQQEKNEYELQKLDKWASLWEWF-NH2
	1675	Ac-WQEWQKITALEQAQIQQEKNEYELQKLDKWASLWEWF-NH2
	1676	Ac-WQEWQKITALLEQAQIQQEKNEYELQKLDKWASLWEWF-NH2
	1677	Ac-WQEWQKITALLEQAQIQQEKNEYELQKLDKWASLWEWF-NH2
	1678	Ac-WQEWQKITALLEQAQIQAEKNEYELQKLDKWASLWEWF-NH2
30	1679	Ac-WQEWQKITALLEQAQIQAEKNEYELQKLDKWASLWEWF-NH2
	1680	Ac-VFPSDEFDASISQVNEKINQSLAFIRKSDELLHNV-NH2
	1681	Ac-VFPSDEFDASISQVNEKINQSLAAIRKSDELLHNV-NH2

T	
No.	Sequence
1682	Ac-VFPSDEFDASISQVNEKINQSLAFIRKSDEALHNV-NH2
1683	Ac-VFPSDEFDASISQVNEKINQSLAFIRKSDELAHNV-NH2
1684	Ac-VFPSDEFDASISQVNEKINQSLAFIRKSDELLANV-NH2
1685	Ac-WQEWQKITALLEQAQIQQAKNEYELQKLDKWASLWEWF-NH2
1687	Ac-WQEWQKITALLEQAQIQQEKNEYELQALDKWASLWEWF-NH2
1688	Ac-WQEWQKITALLEQAQIQQEKNEYELQKADKWASLWEWF-NH2

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5.4. SYNTHESIS OF PEPTIDES

The peptides of the invention may be synthesized or prepared by techniques well known in the art. See, for example, Creighton, 1983, *Proteins: Structures and Molecular Principles*, W.H. Freeman and Co., NY, which is incorporated herein by reference in its entirety. Short peptides, for example, can be synthesized on a solid support or in solution. Longer peptides may be made using recombinant DNA techniques. Here, the nucleotide sequences encoding the peptides of the invention may be synthesized, and/or cloned, and expressed according to techniques well known to those of ordinary skill in the art. See, for example, Sambrook, et al., 1989, *Molecular Cloning, A Laboratory Manual*, Vols. 1-3, Cold Spring Harbor Press, NY.

The peptides of the invention may alternatively be synthesized such that one or more of the bonds which link the amino acid residues of the peptides are non-peptide bonds. These alternative non-peptide bonds may be formed by utilizing reactions well known to those in the art, and may include, but are not limited to imino, ester, hydrazide, semicarbazide, and azo bonds, to name but a few. In yet another embodiment of the invention, peptides comprising the sequences described above may be synthesized with additional chemical groups present at their amino and/or carboxy termini, such that, for example, the stability, bioavailability, and/or inhibitory activity of the peptides is enhanced. For example, hydrophobic groups such as carbobenzoxyl, dansyl, or t-butylloxycarbonyl groups, may be added to the peptides' amino termini. Likewise, an acetyl group or a 9-fluorenylmethoxy-carbonyl group may be placed at the

peptides' amino termini. (See "X" Tables I to IV, above.) Additionally, the hydrophobic group, t-butyloxycarbonyl, or an amido group may be added to the peptides' carboxy termini. (See "Z" in Tables I to IV, above.)

5 Further, the peptides of the invention may be synthesized such that their steric configuration is altered. For example, the D-isomer of one or more of the amino acid residues of the peptide may be used, rather than the usual L-isomer.

10 Still further, at least one of the amino acid residues of the peptides of the invention may be substituted by one of the well known non-naturally occurring amino acid residues. Alterations such as these may serve to increase the stability,
15 bioavailability and/or inhibitory action of the peptides of the invention.

Any of the peptides described above may, additionally, have a macromolecular carrier group covalently attached to their amino and/or carboxy termini. Such macromolecular carrier groups may
20 include, for example, lipid-fatty acid conjugates, polyethylene glycol, carbohydrates or additional peptides. "X", in Tables I to IV, above, may therefore additionally represent any of the above macromolecular carrier groups covalently attached to
25 the amino terminus of a peptide, with an additional peptide group being preferred. Likewise, "Z", in Tables I to IV, may additionally represent any of the macromolecular carrier groups described above.

30 5.5. ASSAYS FOR ANTI-MEMBRANE FUSION ACTIVITY

Described herein, are methods for ability of a compound, such as the peptides of the invention, to

inhibit membrane fusion events. Specifically, assays for cell fusion events are described in Section 5.5.1, below, and assays for antiviral activity are described in Section 5.5.2, below.

5 5.5.1 ASSAYS FOR CELL FUSION EVENTS

Assays for cell fusion events are well known to those of skill in the art, and may be used in conjunction, for example, with the peptides of the invention to test the peptides' antifusogenic capabilities.

10 Cell fusion assays are generally performed in vitro. Such an assay may comprise culturing cells which, in the absence of any treatment would undergo an observable level of syncytial formation. For example, uninfected cells may be incubated in the
15 presence of cells chronically infected with a virus that induces cell fusion. Such viruses may include, but are not limited to, HIV, SIV, or respiratory syncytial virus.

For the assay, cells are incubated in the
20 presence of a peptide to be assayed. For each peptide, a range of peptide concentrations may be tested. This range should include a control culture wherein no peptide has been added.

Standard conditions for culturing cells, well
25 known to those of ordinary skill in the art, are used. After incubation for an appropriate period (24 hours at 37°C, for example) the culture is examined microscopically for the presence of multinucleated giant cells, which are indicative of cell fusion and syncytial formation. Well known stains, such as
30 crystal violet stain, may be used to facilitate the visualization of syncytial formation.

5.5.2 ASSAYS FOR ANTIVIRAL ACTIVITY

The antiviral activity exhibited by the peptides of the invention may be measured, for example, by easily performed in vitro assays, such as those described below, which can test the peptides' ability to inhibit syncytia formation, or their ability to inhibit infection by cell-free virus. Using these assays, such parameters as the relative antiviral activity of the peptides, exhibit against a given strain of virus and/or the strain specific inhibitory activity of the peptide can be determined.

A cell fusion assay may be utilized to test the peptides' ability to inhibit viral-induced, such as HIV-induced, syncytia formation in vitro. Such an assay may comprise culturing uninfected cells in the presence of cells chronically infected with a syncytial-inducing virus and a peptide to be assayed. For each peptide, a range of peptide concentrations may be tested. This range should include a control culture wherein no peptide has been added. Standard conditions for culturing, well known to those of ordinary skill in the art, are used. After incubation for an appropriate period (24 hours at 37°C, for example) the culture is examined microscopically for the presence of multinucleated giant cells, which are indicative of cell fusion and syncytia formation. Well known stains, such as crystal violet stain, may be used to facilitate syncytial visualization. Taking HIV as an example, such an assay would comprise CD-4⁺ cells (such as Molt or CEM cells, for example) cultured in the presence of chronically HIV-infected cells and a peptide to be assayed.

Other well known characteristics of viral infection may also be assayed to test a peptide's

antiviral capabilities. Once again taking HIV as an example, a reverse transcriptase (RT) assay may be utilized to test the peptides' ability to inhibit infection of CD-4⁺ cells by cell-free HIV. Such an assay may comprise culturing an appropriate
5 concentration (i.e., TCID₅₀) of virus and CD-4⁺ cells in the presence of the peptide to be tested. Culture conditions well known to those in the art are used. As above, a range of peptide concentrations may be used, in addition to a control culture wherein no
10 peptide has been added. After incubation for an appropriate period (e.g., 7 days) of culturing, a cell-free supernatant is prepared, using standard procedures, and tested for the presence of RT activity as a measure of successful infection. The RT activity
15 may be tested using standard techniques such as those described by, for example, Goff et al. (Goff, S, et al., 1981, J. Virol. 38:239-248) and/or Willey et al. (Willey, R. et al., 1988, J. Virol. 62:139-147). These references are incorporated herein by reference in their entirety.

20 Standard methods which are well-known to those of skill in the art may be utilized for assaying non-retroviral activity. See, for example, Pringle et al. (Pringle, C.R. et al., 1985, J. Medical Virology 17:377-386) for a discussion of respiratory syncytial
25 virus and parainfluenza virus activity assay techniques. Further, see, for example, "Zinsser Microbiology", 1988, Joklik, W.K. et al., eds., Appleton & Lange, Norwalk, CT, 19th ed., for a general review of such techniques. These references are
30 incorporated by reference herein in their entirety. In addition, the Examples presented below, in Sections

17, 18, 26 and 27 each provide additional assays for the testing of a compound's antiviral capability.

In vivo assays may also be utilized to test, for example, the antiviral activity of the peptides of the invention. To test for anti-HIV activity, for
5 example, the in vivo model described in Barnett et al. (Barnett, S.W. et al., 1994, Science 266:642-646) may be used.

Additionally, anti-RSV activity can be assayed in vivo via well known mouse models. For example, RSV
10 can be administered intranasally to mice of various inbred strains. Virus replicates in lungs of all strains, but the highest titers are obtained in P/N, C57L/N and DBA/2N mice. Infection of BALB/c mice produces an asymptomatic bronchiolitis characterized
15 by lymphocytic infiltrates and pulmonary virus titers of 10^4 to 10^5 pfu/g of lung tissue (Taylor, G. et al., 1984, Infect. Immun. 43:649-655).

Cotton rat models of RSV are also well known. Virus replicates to high titer in the nose and lungs of the cotton rat but produces few if any signs of
20 inflammation.

5.6. USES OF THE PEPTIDES OF THE INVENTION

The peptides of the invention may be utilized as antifusogenic or antiviral compounds, or as compounds
25 which modulate intracellular processes involving coiled coil peptide structures. Further, such peptides may be used to identify agents which exhibit antifusogenic, antiviral or intracellular modulatory activity. Still further, the peptides of the
invention may be utilized as organism or viral
30 type/subtype-specific diagnostic tools.

The antifusogenic capability of the peptides of the invention may additionally be utilized to inhibit or treat/ameliorate symptoms caused by processes involving membrane fusion events. Such events may include, for example, virus transmission via cell-cell
5 fusion, abnormal neurotransmitter exchange via cell-fusion, and sperm-egg fusion. Further, the peptides of the invention may be used to inhibit free viral, such as retroviral, particularly HIV, transmission to uninfected cells wherein such viral infection involves
10 membrane fusion events or involves fusion of a viral structure with a cell membrane. Among the intracellular disorders involving coiled coil peptides structures which may be ameliorated by the peptides of the invention are disorders involving, for example,
15 bacterial toxins.

With respect to antiviral activity, the viruses whose transmission may be inhibited by the peptides of the invention include, but are not limited to human retroviruses, such as HIV-1 and HIV-2 and the human T-lymphocyte viruses (HTLV-I and II), and non-human
20 retroviruses such as bovine leukosis virus, feline sarcoma and leukemia viruses, simian immunodeficiency, sarcoma and leukemia viruses, and sheep progress pneumonia viruses.

Non retroviral viruses whose transmission may be
25 inhibited by the peptides of the invention include, but are not limited to human respiratory syncytial virus, canine distemper virus, newcastle disease virus, human parainfluenza virus, influenza viruses, measles viruses, Epstein-Barr viruses, hepatitis B
30 viruses, and simian Mason-Pfizer viruses.

Non enveloped viruses whose transmission may be inhibited by the peptides of the invention include,

but are not limited to picornaviruses such as polio viruses, hepatitis A virus, enterovirus, echoviruses and coxsackie viruses, papovaviruses such as papilloma virus, parvoviruses, adenoviruses and reoviruses.

As discussed more fully, below, in Section 5.6.1
5 and in the Example presented, below, in Section 8,
DP107, DP178, DP107 analog and DP178 analog peptides
form non-covalent protein-protein interactions which
are required for normal activity of the virus. Thus,
the peptides of the invention may also be utilized as
10 components in assays for the identification of
compounds that interfere with such protein-protein
interactions and may, therefore, act as antiviral
agents. These assays are discussed, below, in Section
5.6.1.

As demonstrated in the Example presented below in
15 Section 6, the antiviral activity of the peptides of
the invention may show a pronounced type and subtype
specificity, i.e., specific peptides may be effective
in inhibiting the activity of only specific viruses.
This feature of the invention presents many
20 advantages. One such advantage, for example, lies in
the field of diagnostics, wherein one can use the
antiviral specificity of the peptide of the invention
to ascertain the identity of a viral isolate. With
respect to HIV, one may easily determine whether a
25 viral isolate consists of an HIV-1 or HIV-2 strain.
For example, uninfected CD-4⁺ cells may be co-infected
with an isolate which has been identified as
containing HIV the DP178 (SEQ ID:1) peptide, after
which the retroviral activity of cell supernatants may
30 be assayed, using, for example, the techniques
described above in Section 5.2. Those isolates whose
retroviral activity is completely or nearly completely

inhibited contain HIV-1. Those isolates whose viral activity is unchanged or only reduced by a small amount, may be considered to not contain HIV-1. Such an isolate may then be treated with one or more of the other DP178 peptides of the invention, and
5 subsequently be tested for its viral activity in order to determine the identify of the viral isolate. The DP107 and DP178 analogs of the invention may also be utilized in a diagnostic capacity specific to the type and subtype of virus or organism in which the specific
10 peptide sequence is found. A diagnostic procedure as described, above, for DP178, may be used in conjunction with the DP107/DP178 analog of interest.

5.6.1. SCREENING ASSAYS

15 As demonstrated in the Example presented in Section 8, below, DP107 and DP178 portions of the TM protein gp41, i.e., the HR1 and HR2 portions of gp41, respectively, form non-covalent protein-protein interactions. As is also demonstrated, the maintenance of such interactions is necessary for
20 normal viral infectivity. Thus, compounds which bind DP107, bind DP178, and/or act to disrupt normal DP107/DP178 protein-protein interactions may act as antifusogenic, antiviral or cellular modulatory agents. Described below are assays for the
25 identification of such compounds. Note that, while, for ease and clarity of discussion, DP107 and DP178 peptides will be used as components of the assays described, but it is to be understood that any of the DP107 analog or DP178 analog peptides described,
30 above, in Sections 5.1 through 5.3 may also be utilized as part of these screens for compounds.

For example, in certain embodiments the assays of the invention may be use DP107 and/or DP178 analogs that contain one or more amino acid residue truncations, deletions, insertions or substitutions. In particular, in one preferred embodiment, the DP107, DP178, DP107-like and DP178-like peptides can comprise amino and/or carboxy-terminal insertions corresponding to about two to about fifty amino acids amino-to or carboxy-to the endogenous sequence from which the DP107, DP178, DP107-like or DP178-like peptide is derived. In another particular embodiment, the peptides used in the assays described herein further comprise additional, heterologous sequence useful for detecting, immobilizing and/or purifying the particular peptide. Such heterologous sequences include, but are not limited to maltose binding fusion proteins containing a DP178, DP107, DP178-like or DP107-like sequence such as the M41Δ178 and MF5.1 maltose binding fusion proteins described in Sections 8 and 30, below.

In certain embodiments, such analogs will have reduced binding affinities and are therefore useful, e.g., to screen for compounds which inhibit the formation of or, alternatively, disrupt complexes between DP107/DP178 complexes. Among such reduced binding analogs are peptides exhibiting one or more alanine insertion or substitutions, including, e.g., the peptides described in the examples presented in Sections 30 and 31, below. It is understood that such analogs which have reduced binding affinities, including the analogs described in Sections 30 and 31 below, are also part of the present invention.

Compounds which may be tested for an ability to bind DP107, DP178, and/or disrupt DP107/DP178 interactions, and which therefore, potentially represent antifusogenic, antiviral or intracellular modulatory compounds, include, but are not limited to, peptides made of D- and/or L-configuration amino acids (in, for example, the form of random peptide libraries; see Lam, K.S. et al., 1991, Nature 354:82-84), phosphopeptides (in, for example, the form of random or partially degenerate, directed phosphopeptide libraries; see, for example, Songyang, Z. et al., 1993, Cell 72:767-778), antibodies, and small organic or inorganic molecules. Synthetic compounds, natural products, and other sources of potentially effective materials may be screened in a variety of ways, as described in this Section.

Compounds that can be screened, tested and identified as modulating HR1/HR2, DP178/DP107 and/or DP178-like/DP107-like interactions utilizing the methods described herein can, in general, include, e.g., small molecules that are of a molecular weight up to about 1500 daltons. Test compounds, including small molecules, can include, but are not limited to, compounds obtained from any commercial source, including Aldrich (1001 West St. Paul Ave., Milwaukee, WI 53233), Sigma Chemical (P.O. Box 14508, St. Louis, MO 63178), Fluka Chemie AG (Industriestrasse 25, CH-9471 Buchs, Switzerland (Fluka Chemical Corp. 980 South 2nd Street, Ronkonkoma, NY 11779)), Eastman Chemical Company, Fine Chemicals (P.O. Box 431, Kingsport, TN 37662), Boehringer Mannheim GmbH (Sandhofer Strasse 116, D-68298 Mannheim), Takasago (4 Volvo Drive, Rockleigh, NJ 07647), SST Corporation

(635 Brighton Road, Clifton, NJ 07012), Ferro (111 West Irene Road, Zachary, LA 70791), Riedel-deHaen Aktiengesellschaft (P.O. Box D-30918, Seelze, Germany), PPG Industries Inc., Fine Chemicals (One PPG Place, 34th Floor, Pittsburgh, PA 15272). Further any
5 kind of natural products may be screened using the methods of the invention, including microbial, fungal or plant extracts.

Furthermore, diversity libraries of test compounds, including small molecule test compounds,
10 may be commercially obtained from Specs and BioSpecs B.V. (Rijswijk, The Netherlands), Chembridge Corporation (San Diego, CA), Contract Service Company (Dolgoprudny, Moscow Region, Russia), Comgenex USA
Inc. (Princeton, NJ), Maybridge Chemicals Ltd.
15 (Cornwall PL34 OHW, United Kingdom), and Asinex (Moscow, Russia). Combinatorial libraries of test compounds, including small molecule test compounds, can be may be generated as disclosed in Eichler & Houghten, 1995, *Mol. Med. Today* 1:174-180; Dolle,
20 1997, *Mol. Divers.* 2:223-236; Lam, 1997, *Anticancer Drug Des.* 12:145-167. These references are incorporated hereby by reference in their entirety. It is to be noted that such references also teach additional screening methods which may be employed for
25 the further testing of compounds identified via the methods of the invention and which can aid in identifying and isolating compounds which can represent leads and therapeutic compounds.

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The compounds, antibodies, or other molecules identified may be tested, for example, for an ability to inhibit cell fusion or viral activity, utilizing, for example, assays such as those described, above, in Section 5.5.

5 Among the peptides which may be tested are soluble peptides comprising DP107 and/or DP178 domains, and peptides comprising DP107 and/or DP178 domains having one or more mutations within one or both of the domains, such as the M41-P peptide
10 described, below, in the Example presented in Section 8, which contains a isoleucine to proline mutation within the DP178 sequence.

 In one embodiment of such screening methods is a method for identifying a compound to be tested for
15 antiviral ability comprising:

- 1 exposing at least one compound to a peptide comprising a DP107 peptide for a time sufficient to allow binding of the compound to the DP107 peptide;
- 2 removing non-bound compounds; and
- 20 3 determining the presence of the compound bound to the DP107 peptide, thereby identifying an agent to be tested for antiviral ability.

 In a second embodiment of such screening methods
25 is a method for identifying a compound to be tested for antiviral ability comprising:

- (a) exposing at least one compound to a peptide comprising a DP178 peptide for a time sufficient to allow binding of the compound to the DP178 peptide;
- 30 (b) removing non-bound compounds; and

(c) determining the presence of the compound bound to the DP178 peptide, thereby identifying an agent to be tested for antiviral ability.

One method utilizing these types of approaches that may be pursued in the isolation of such DP107-binding or DP178-binding compounds is an assay which would include the attachment of either the DP107 or the DP178 peptide to a solid matrix, such as, for example, agarose or plastic beads, microtiter plate wells, petri dishes, or membranes composed of, for example, nylon or nitrocellulose. In such an assay system, either the DP107 or DP178 protein may be anchored onto a solid surface, and the compound, or test substance, which is not anchored, is labeled, either directly or indirectly (e.g., with a radioactive label such as ^{125}I , an absorption label such as biotin, or a fluorescent label such as fluorescein or rhodamine). In practice, microtiter plates are conveniently utilized. The anchored component may be immobilized by non-covalent or covalent attachments. Non-covalent attachment may be accomplished simply by coating the solid surface with a solution of the protein and drying. Alternatively, an immobilized antibody, preferably a monoclonal antibody, specific for the protein may be used to anchor the protein to the solid surface. The surfaces may be prepared in advance and stored.

In order to conduct the assay, the labeled compound is added to the coated surface containing the anchored DP107 or DP178 peptide. After the reaction is complete, unreacted components are removed (e.g., by washing) under conditions such that any complexes

formed will remain immobilized on the solid surface. The detection of complexes anchored on the solid surface can be accomplished in a number of ways. Where the compound is pre-labeled, the detection of label immobilized on the surface indicates that
5 complexes were formed. Where the labeled component is not pre-labeled, an indirect label can be used to detect complexes anchored on the surface; e.g., using a labeled antibody specific for the compound (the antibody, in turn, may be directly labeled or
10 indirectly labeled with a labeled anti-Ig antibody).

Alternatively, such an assay can be conducted in a liquid phase, the reaction products separated from unreacted components, and complexes detected; e.g., using an immobilized antibody specific for DP107 or
15 DP178, whichever is appropriate for the given assay, or an antibody specific for the compound, i.e., the test substance, in order to anchor any complexes formed in solution, and a labeled antibody specific for the other member of the complex to detect anchored complexes.

20 By utilizing procedures such as this, large numbers of types of molecules may be simultaneously screened for DP107 or DP178-binding capability, and thus potential antiviral activity.

Further, compounds may be screened for an ability
25 to inhibit the formation of or, alternatively, disrupt DP107/DP178 complexes. Such compounds may then be tested for antifusogenic, antiviral or intercellular modulatory capability. For ease of description, DP107 and DP178 will be referred to as "binding partners."
30 Compounds that disrupt such interactions may exhibit antiviral activity. Such compounds may include, but

are not limited to molecules such as antibodies, peptides, and the like described above.

The basic principle of the assay systems used to identify compounds that interfere with the interaction between the DP107 and DP178 peptides involves
5 preparing a reaction mixture containing peptides under conditions and for a time sufficient to allow the two peptides to interact and bind, thus forming a complex. In order to test a compound for disruptive activity, the reaction is conducted in the presence and absence
10 of the test compound, i.e., the test compound may be initially included in the reaction mixture, or added at a time subsequent to the addition of one of the binding partners; controls are incubated without the test compound or with a placebo. The formation of any
15 complexes between the binding partners is then detected. The formation of a complex in the control reaction, but not in the reaction mixture containing the test compound indicates that the compound interferes with the interaction of the DP107 and DP178 peptides.

20 The assay for compounds that interfere with the interaction of the binding partners can be conducted in a heterogeneous or homogeneous format. Heterogeneous assays involve anchoring one of the binding partners onto a solid phase and detecting
25 complexes anchored on the solid phase at the end of the reaction. In homogeneous assays, the entire reaction is carried out in a liquid phase. In either approach, the order of addition of reactants can be varied to obtain different information about the compounds being tested. For example, test compounds
30 that interfere with the interaction between the binding partners, e.g., by competition, can be

identified by conducting the reaction in the presence of the test substance; i.e., by adding the test substance to the reaction mixture prior to or simultaneously with the binding partners. On the other hand, test compounds that disrupt preformed
5 complexes, e.g. compounds with higher binding constants that displace one of the binding partners from the complex, can be tested by adding the test compound to the reaction mixture after complexes have been formed. The various formats are described
10 briefly below.

In a heterogeneous assay system, one binding partner, e.g., either the DP107 or DP178 peptide, is anchored onto a solid surface, and its binding partner, which is not anchored, is labeled, either
15 directly or indirectly (e.g., with a radioactive label such as ^{125}I , an absorption label such as biotin, or a fluorescent label such as fluorescein or rhodamine). In practice, microtiter plates are conveniently utilized. The anchored species may be immobilized by non-covalent or covalent attachments. Non-covalent
20 attachment may be accomplished simply by coating the solid surface with a solution of the protein and drying. Alternatively, an immobilized antibody specific for the protein may be used to anchor the protein to the solid surface. The surfaces may be
25 prepared in advance and stored.

In order to conduct the assay, the binding partner of the immobilized species is added to the coated surface with or without the test compound. After the reaction is complete, unreacted components
30 are removed (e.g., by washing) and any complexes formed will remain immobilized on the solid surface.

The detection of complexes anchored on the solid surface can be accomplished in a number of ways. Where the binding partner was pre-labeled, the detection of label immobilized on the surface indicates that complexes were formed. Where the
5 binding partner is not pre-labeled, an indirect label can be used to detect complexes anchored on the surface; e.g., using a labeled antibody specific for the binding partner (the antibody, in turn, may be directly labeled or indirectly labeled with a labeled
10 anti-Ig antibody). Depending upon the order of addition of reaction components, test compounds which inhibit complex formation or which disrupt preformed complexes can be detected.

Alternatively, the reaction can be conducted in a liquid phase in the presence or absence of the test
15 compound, the reaction products separated from unreacted components, and complexes detected; e.g., using an immobilized antibody specific for one binding partner to anchor any complexes formed in solution, and a labeled antibody specific for the other binding
20 partner to detect anchored complexes. Again, depending upon the order of addition of reactants to the liquid phase, test compounds which inhibit complex or which disrupt preformed complexes can be identified.

25 In an alternate embodiment of the invention, a homogeneous assay can be used. In this approach, a preformed complex of the DP107 and DP178 peptides is prepared in which one of the binding partners is labeled, but the signal generated by the label is quenched due to complex formation (see, e.g., U.S.
30 Patent No. 4,109,496 by Rubenstein which utilizes this approach for immunoassays). The addition of a test

substance that competes with and displaces one of the binding partners from the preformed complex will result in the generation of a signal above background. In this way, test substances which disrupt DP-107/DP-178 protein-protein interaction can be identified.

5 In still another embodiment of the invention, fluorescence polarization may be used in a homogenous assay. In this approach, complex formation is detected by measuring the polarization of a fluorescently labeled peptide (e.g., with fluorescein
10 or rhodamine) in a sample. Binding of the peptide to its complementary HR1 or HR2 binding domain in a larger molecular weight peptide or protein, such as in a maltose binding fusion protein described herein, alters the correlation time of the fluorescent moiety
15 and thereby decreases the fluorescence polarization of the labeled peptide.

In an alternative screening assay, test compounds may be assayed for their ability to disrupt a DP178/DP107 interaction, as measured immunometrically using an antibody specifically reactive to a
20 DP107/DP178 complex (i.e., an antibody that recognizes neither DP107 nor DP178 individually). Such an assay acts as a competition assay, and is based on techniques well known to those of skill in the art.

The above competition assay may be described, by
25 way of example, and not by way of limitation, by using the DP178 and M41Δ178 peptides and by assaying test compounds for the disruption of the complexes formed by these two peptides by immunometrically visualizing DP178/M41Δ178 complexes via the human recombinant Fab, Fab-d, as described, below, in the Example presented
30 in Section 8. M41Δ178 is a maltose binding fusion

protein containing a gp41 region having its DP178 domain deleted, and is described, below, in the Example presented in Section 8.

Utilizing such an assay, M41Δ178 may be immobilized onto solid supports such as microtiter wells. A series of dilutions of a test compound may then be added to each M41Δ178-containing well in the presence of a constant concentration of DP-178 peptide. After incubation, at, for example, room temperature for one hour, unbound DP-178 and test compound are removed from the wells and wells are then incubated with the DP178/M41Δ178-specific Fab-d antibody. After incubation and washing, unbound Fab-d is removed from the plates and bound Fab-d is quantitated. A no-inhibitor control should also be conducted. Test compounds showing an ability to disrupt DP178/M41Δ178 complex formation are identified by their concentration-dependent decrease in the level of Fab-d binding.

A variation of such an assay may be utilized to perform a rapid, high-throughput binding assay which is capable of directly measuring DP178 binding to M41Δ178 for the determination of binding constants of the ligand or inhibitory constants for competitors of DP178 binding.

Such an assay takes advantage of accepted radioligand and receptor binding principles. (See, for example, Yamamura, H.I. et al., 1985, "Neurotransmitter Receptor Binding", 2nd ed., Raven Press, NY.) As above, M41Δ178 is immobilized onto a solid support such as a microtiter well. DP178 binding to M41Δ178 is then quantitated by measuring the fraction of DP178 that is bound as ¹²⁵I-DP178 and calculating the total amount bound using a value for

specific activity (dpm/ μ g peptide) determined for each labeled DP178 preparation. Specific binding to M41 Δ 178 is defined as the difference of the binding of the labeled DP178 preparation in the microtiter wells (totals) and the binding in identical wells
5 containing, in addition, excess unlabeled DP178 (nonspecifics).

Because the binding affinity for native DP178 and DP107 is very high (including native DP178-like and DP107-like peptides from other species; e.g., 10 nM
10 for DP178 in HIV-1, and 2 nM for T112 in RSV), test compounds must exhibit high binding properties to interfere with or disrupt the DP178/DP107 binding interaction. Accordingly, in another non-limiting example of the above-described competitions assays,
15 such assays can be performed using "modified" DP107 and/or DP178 peptides (e.g., DP107 and/or DP178 analogs) which have reduced binding affinities relative to the unmodified "parent peptides". The use of such modified DP107 and DP178 peptides greatly increases the sensitivity of the competition assays of
20 the invention by identifying more compounds with inhibitory potential. The binding affinities of compounds identified in the assays can then be optimized, e.g., using standard medicinal chemistry techniques, to generate compounds that are more
25 powerful inhibitors of DP107/DP178 complex formation and are therefore useful, e.g., as antiviral reagents. Alternatively, compounds identified in the competition assays using DP107 and/or DP178 analogs with reduced binding affinities may, themselves, be useful, e.g.,
30 as antiviral reagents.

The term "reduced affinity," as used herein, refers to a DP107, DP178, DP107-like or DP178-like peptide that interacts with and forms a DP107/DP178 peptide pair, a HR1/DP178 pair or an HR2/DP107 pair under competition assay conditions, but interacts with
5 its "partner" to form such a pair with a lower affinity than would a DP107 or DP178 "parent" peptide from which the reduced affinity peptide is derived.

Generally, the binding affinity of a peptide can be expressed as a B_{50} value, i.e., the concentration of
10 peptide necessary for 50% of the peptide molecules to bind to their target under a given set of conditions. Preferably, the B_{50} value of a reduced affinity peptide will be at least twice, and more preferably at least five times, at least 10 times, at least 20 times, or
15 at least 100 times the B_{50} value of the unmodified peptide from which it was derived.

Modified DP107 and DP178 peptides that have reduced binding affinities may be generated according to any number of techniques that will be readily apparent to those skilled in the art. For example, in
20 one embodiment modified DP107 and DP178 peptides with reduced binding affinities may be generated by generating truncated DP107 and DP178 peptides, respectively. Such peptides may be routinely synthesized and tested, e.g., by the above described
25 screening assays, to determine their binding affinities to their target. For example, as described in the example presented below in Section 30, reducing the length of the native RSV DP178-like peptide T112 from 35 to 28 amino acid residues resulted in a five
30 fold drop in binding affinity (from 1 nM to 5 nM).

Generally, such truncation can be of 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid residues.

Alternatively, modified DP107 and DP178 peptides with reduced binding affinity may be identified and generated by identifying and substituting, inserting or deleting amino acid residues. For example in one embodiment, which is also demonstrated in the example presented below in Section 30, modified DP107 and/or DP178 peptides may be routinely synthesized and assayed for reduced binding affinity by systematically replacing one or more amino acid residues of the native DP107 or DP178 peptide with other amino acid residues and testing the binding affinity of the resulting peptide by techniques such as those described herein. Preferably, the substituted amino acid residues are neutral amino acid residues exhibiting relatively small side chains, such as alanine or glycine.

Such substitutions can identify "key" amino acid residues and can be used in the competition assays of the invention. Alternatively, upon identification of key residues by such systematic substitutions, the key residues can be changed to other residues and the resulting, modified peptides can be tested for binding affinity.

Modified DP107 and/or DP178 peptides that have reduced binding affinities may still further be identified using principles of protein chemistry and design that are well known to those of skill in the art. Specifically, such principles may be used to identify those amino acid residues of a native DP107 or DP178 sequence that effect, e.g., solubility, binding affinity, or stability of the peptide. Thus,

for example, using known principles of amino acid chemistry and protein design one skilled in the art could identify amino acid residues in a native DP107 or DP178 peptide that affect the structure of the peptide.

5

5.7 PHARMACEUTICAL FORMULATIONS, DOSAGES AND MODES OF ADMINISTRATION

The peptides of the invention may be administered using techniques well known to those in the art. Preferably, agents are formulated and administered systemically. Techniques for formulation and administration may be found in "Remington's Pharmaceutical Sciences", 18th ed., 1990, Mack Publishing Co., Easton, PA. Suitable routes may include oral, rectal, transmucosal, or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as, intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, or intraocular injections, just to name a few. For injection, the agents of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiological saline buffer. For such transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

In instances wherein intracellular administration of the peptides of the invention or other inhibitory agents is preferred, techniques well known to those of ordinary skill in the art may be utilized. For example, such agents may be encapsulated into

liposomes, then administered as described above. Liposomes are spherical lipid bilayers with aqueous interiors. All molecules present in an aqueous solution at the time of liposome formation are incorporated into the aqueous interior. The liposomal
5 contents are both protected from the external microenvironment and, because liposomes fuse with cell membranes, are effectively delivered into the cell cytoplasm. Additionally, due to their hydrophobicity, when small molecules are to be administered, direct
10 intracellular administration may be achieved.

Nucleotide sequences encoding the peptides of the invention which are to be intracellularly administered may be expressed in cells of interest, using techniques well known to those of skill in the art. For example, expression vectors derived from viruses
15 such as retroviruses, vaccinia viruses, adeno-associated viruses, herpes viruses, or bovine papilloma viruses, may be used for delivery and expression of such nucleotide sequences into the targeted cell population. Methods for the
20 construction of such vectors and expression constructs are well known. See, for example, Sambrook et al., 1989, Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, Cold Spring Harbor NY, and Ausubel et al., 1989, Current Protocols in Molecular
25 Biology, Greene Publishing Associates and Wiley Interscience, NY.

With respect to HIV, peptides of the invention, particularly DP107 and DP178, may be used as therapeutics in the treatment of AIDS. In addition,
30 the peptides may be used as prophylactic measures in previously uninfected individuals after acute exposure to an HIV virus. Examples of such prophylactic use of

the peptides may include, but are not limited to, prevention of virus transmission from mother to infant and other settings where the likelihood of HIV transmission exists, such as, for example, accidents in health care settings wherein workers are exposed to
5 HIV-containing blood products. The successful use of such treatments do not rely upon the generation of a host immune response directed against such peptides.

Effective dosages of the peptides of the invention to be administered may be determined through
10 procedures well known to those in the art which address such parameters as biological half-life, bioavailability, and toxicity. Given the data presented below in Section 6, DP178, for example, may prove efficacious in vivo at doses required to achieve circulating levels of about 1 to about 10 ng per ml of
15 peptide.

A therapeutically effective dose refers to that amount of the compound sufficient to result in amelioration of symptoms or a prolongation of survival in a patient. Toxicity and therapeutic efficacy of
20 such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the
25 population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD₅₀/ED₅₀. Compounds which exhibit large therapeutic indices are preferred. The data obtained from these cell culture assays and animal studies can be used in formulating a range of
30 dosage for use in humans. The dosage of such compounds lies preferably within a range of

circulating concentrations that include the ED₅₀ with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the IC₅₀ (e.g., the concentration of the test compound which achieves a half-maximal inhibition of the fusogenic event, such as a half-maximal inhibition of viral infection relative to the amount of the event in the absence of the test compound) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography (HPLC).

The peptides of the invention may, further, serve the role of a prophylactic vaccine, wherein the host raises antibodies against the peptides of the invention, which then serve to neutralize HIV viruses by, for example, inhibiting further HIV infection.

Administration of the peptides of the invention as a prophylactic vaccine, therefore, would comprise administering to a host a concentration of peptides effective in raising an immune response which is sufficient to neutralize HIV, by, for example, inhibiting HIV ability to infect cells. The exact concentration will depend upon the specific peptide to be administered, but may be determined by using standard techniques for assaying the development of an immune response which are well known to those of

ordinary skill in the art. The peptides to be used as vaccines are usually administered intramuscularly.

The peptides may be formulated with a suitable adjuvant in order to enhance the immunological response. Such adjuvants may include, but are not
5 limited to mineral gels such as aluminum hydroxide; surface active substances such as lysolecithin, pluronic polyols, polyanions; other peptides; oil emulsions; and potentially useful human adjuvants such as BCG and *Corynebacterium parvum*. Many methods may
10 be used to introduce the vaccine formulations described here. These methods include but are not limited to oral, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, and intranasal routes.

Alternatively, an effective concentration of
15 polyclonal or monoclonal antibodies raised against the peptides of the invention may be administered to a host so that no uninfected cells become infected by HIV. The exact concentration of such antibodies will vary according to each specific antibody preparation,
20 but may be determined using standard techniques well known to those of ordinary skill in the art. Administration of the antibodies may be accomplished using a variety of techniques, including, but not limited to those described in this section.

For all such treatments described above, the
25 exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (See e.g. Fingl et al., 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 p1).
30

It should be noted that the attending physician would know how to and when to terminate, interrupt, or

adjust administration due to toxicity, or to organ dysfunctions. Conversely, the attending physician would also know to adjust treatment to higher levels if the clinical response were not adequate (precluding toxicity). The magnitude of an administered dose in
5 the management of the oncogenic disorder of interest will vary with the severity of the condition to be treated and the route of administration. The dose and perhaps dose frequency, will also vary according to the age, body weight, and response of the individual
10 patient. A program comparable to that discussed above may be used in veterinary medicine.

Use of pharmaceutically acceptable carriers to formulate the compounds herein disclosed for the practice of the invention into dosages suitable for
15 systemic administration is within the scope of the invention. With proper choice of carrier and suitable manufacturing practice, the compositions of the present invention, in particular, those formulated as solutions, may be administered parenterally, such as by intravenous injection. The compounds can be
20 formulated readily using pharmaceutically acceptable carriers well known in the art into dosages suitable for oral administration. Such carriers enable the compounds of the invention to be formulated as tablets, pills, capsules, liquids, gels, syrups,
25 slurries, suspensions and the like, for oral ingestion by a patient to be treated.

Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an effective
30 amount to achieve its intended purpose. Determination of the effective amounts is well within the capability

of those skilled in the art, especially in light of the detailed disclosure provided herein.

In addition to the active ingredients, these pharmaceutical compositions may contain suitable pharmaceutically acceptable carriers comprising
5 excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. The preparations formulated for oral administration may be in the form of tablets, dragees, capsules, or solutions.

10 The pharmaceutical compositions of the present invention may be manufactured in a manner that is itself known, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

15 Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable
20 lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such
25 as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

30 Pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipient, optionally grinding a resulting mixture,

and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, 5 for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be 10 added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, 15 polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize 20 different combinations of active compound doses.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The 25 push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, 30 liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added.

6. EXAMPLE: DP178 (SEQ ID:1) IS A POTENT
INHIBITOR OF HIV-1 INFECTION

In this example, DP178 (SEQ ID:1) is shown to be a potent inhibitor of HIV-1 mediated CD-4⁺ cell-cell fusion and infection by cell free virus. In the fusion assay, this peptide completely blocks virus induced syncytia formation at concentrations of from 1-10 ng/ml. In the infectivity assay the inhibitory concentration is somewhat higher, blocking infection at 90ng/ml. It is further shown that DP178 (SEQ ID:1) shows that the antiviral activity of DP178 (SEQ ID:1) is highly specific for HIV-1. Additionally, a synthetic peptide, DP-185 (SEQ ID:3), representing a HIV-1-derived DP178 homolog is also found to block HIV-1-mediated syncytia formation.

6.1. MATERIALS AND METHODS

6.1.1. PEPTIDE SYNTHESIS

Peptides were synthesized using Fast Moc chemistry on an Applied Biosystems Model 431A peptide synthesizer. Generally, unless otherwise noted, the peptides contained amidated carboxy termini and acetylated amino termini. Amidated peptides were prepared using Rink resin (Advanced Chemtech) while peptides containing free carboxy termini were synthesized on Wang (p-alkoxy-benzyl-alcohol) resin (Bachem). First residues were double coupled to the appropriate resin and subsequent residues were single coupled. Each coupling step was followed by acetic anhydride capping. Peptides were cleaved from the resin by treatment with trifluoroacetic acid (TFA) (10ml), H₂O (0.5ml), thioanisole (0.5ml), ethanedithiol (0.25ml), and crystalline phenol (0.75g). Purifi-

cation was carried out by reverse phase HPLC. Approximately 50mg samples of crude peptide were chromatographed on a Waters Delta Pak C18 column (19mm x 30cm, 15 μ spherical) with a linear gradient; H₂O/acetonitrile 0.1% TFA. Lyophilized peptides were
5 stored desiccated and peptide solutions were made in water at about 1mg/ml. Electrospray mass spectrometry yielded the following results: DP178 (SEQ
ID:1):4491.87 (calculated 4491.94); DP-180 (SEQ
ID:2):4491.45 (calculated 4491.94); DP-185 (SEQ
10 ID:3):not done (calculated 4546.97).

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6.1.2. VIRUS

The HIV-1_{LAI} virus was obtained from R. Gallo (Popovic, M. et al., 1984, Science 224:497-508) and propagated in CEM cells cultured in RPMI 1640
5 containing 10% fetal calf serum. Supernatant from the infected CEM cells was passed through a 0.2 μ m filter and the infectious titer estimated in a microinfectivity assay using the AA5 cell line to support virus replication. For this purpose, 25 μ l of
10 serial diluted virus was added to 75 μ l AA5 cells at a concentration of 2×10^5 /ml in a 96-well microtitre plate. Each virus dilution was tested in triplicate. Cells were cultured for eight days by addition of fresh medium every other day. On day 8 post
15 infection, supernatant samples were tested for virus replication as evidenced by reverse transcriptase activity released to the supernatant. The TCID₅₀ was calculated according to the Reed and Muench formula (Reed, L.J. et al., 1938, Am. J. Hyg. 27:493-497). The titer of the HIV-1_{LAI} and HIV-1_{MN} stocks used for
20 these studies, as measured on the AA5 cell line, was approximately 1.4×10^6 and 3.8×10^4 TCID₅₀/ml, respectively.

6.1.3. CELL FUSION ASSAY

Approximately 7×10^4 Molt cells were incubated
25 with 1×10^4 CEM cells chronically infected with the HIV-1_{LAI} virus in 96-well plates (one-half area cluster plates; Costar, Cambridge, MA) in a final volume of 100 μ l culture medium as previously described (Matthews, T.J. et al., 1987, Proc. Natl. Acad. Sci. USA 84: 5424-5428). Peptide inhibitors were added in
30 a volume of 10 μ l and the cell mixtures were incubated for 24 hr. at 37°C. At that time, multinucleated

giant cells were estimated by microscopic examination at a 40x magnification which allowed visualization of the entire well in a single field.

6.1.4. CELL FREE VIRUS INFECTION ASSAY

5 Synthetic peptides were incubated at 37°C with either 247 TCID₅₀ (for experiment depicted in FIG. 2), or 62 TCID₅₀ (for experiment depicted in FIG.3) units of HIV-1_{LAI} virus or 25 TCID₅₀ units of HIV-2_{NIH2} and CEM CD4⁺ cells at peptide concentrations of 0, 0.04, 0.4, 10 4.0, and 40µg/ml for 7 days. The resulting reverse transcriptase (RT) activity in counts per minute was determined using the assay described, below, in Section 6.1.5. See, Reed, L.J. et al., 1938, Am. J. Hyg. 27: 493-497 for an explanation of TCID₅₀ 15 calculations.

6.1.5. REVERSE TRANSCRIPTASE ASSAY

The micro-reverse transcriptase (RT) assay was adapted from Goff et al. (Goff, S. et al., 1981, J. Virol. 38:239-248) and Willey et al. (Willey, R. et al., 1988, J. Virol. 62:139-147). Supernatants from 20 virus/cell cultures are adjusted to 1% Triton-X100. A 10µl sample of supernatant was added to 50µl of RT cocktail in a 96-well U-bottom microtitre plate and the samples incubated at 37°C for 90 min. The RT 25 cocktail contained 75mM KCl, 2mM dithiothreitol, 5mM MgCl₂, 5µg/ml poly A (Pharmacia, cat. No. 27-4110-01), 0.25 units/ml oligo dT (Pharmacia, cat. No. 27-7858-01), 0.05% NP40, 50mM Tris-HCl, pH 7.8, 0.5µM non-radioactive dTTP, and 10µCi/ml ³²P-dTTP (Amersham, cat. No. PB.10167). 30

After the incubation period, 40µl of reaction mixture was applied to a Schleicher and Schuell (S+S)

NA45 membrane (or DE81 paper) saturated in 2 x SSC buffer (0.3M NaCl and 0.003M sodium citrate) held in a S+S Minifold over one sheet of GB003 (S+S) filter paper, with partial vacuum applied. Each well of the minifold was washed four times with 200 μ l 2xSSC, under
5 full vacuum. The membrane was removed from the minifold and washed 2 more times in a pyrex dish with an excess of 2xSSC. Finally, the membrane was drained on absorbent paper, placed on Whatman #3 paper, covered with Saran wrap, and exposed to film overnight
10 at -70°C.

6.2. RESULTS

6.2.1. PEPTIDE INHIBITION OF INFECTED CELL- INDUCED SYNCYTIA FORMATION

The initial screen for antiviral activity assayed
15 peptides' ability to block syncytium formation induced by overnight co-cultivation of uninfected Molt4 cells with chronically HIV-1 infected CEM cells. The results of several such experiments are presented herein. In the first of these experiments, serial
20 DP178 (SEQ ID:1) peptide concentrations between 10 μ g/ml and 12.5ng/ml were tested for blockade of the cell fusion process. For these experiments, CEM cells chronically infected with either HIV-1_{LAI}, HIV-1_{MN}, HIV-1_{RF}, or HIV-1_{SF2} virus were cocultivated overnight with
25 uninfected Molt 4 cells. The results (FIG. 4) show that DP178 (SEQ ID:1) afforded complete protection against each of the HIV-1 isolates down to the lowest concentration of DP178 (SEQ ID:1) used. For HIV_{LAI} inhibition, the lowest concentration tested was
12.5ng/ml; for all other HIV-1 viruses, the lowest
30 concentration of DP178 (SEQ ID:1) used in this study was 100ng/ml. A second peptide, DP-180 (SEQ ID:2),

containing the same amino acid residues as DP178 (SEQ ID:1) but arranged in a random order exhibited no evidence of anti-fusogenic activity even at the high concentration of 40 μ g/ml (FIG. 4). These observations indicate that the inhibitory effect of DP178 (SEQ ID:1) is primary sequence-specific and not related to non-specific peptide/protein interactions. The actual endpoint (*i.e.*, the lowest effective inhibitory concentration) of DP178 inhibitory action is within the range of 1-10 ng/ml.

10 The next series of experiments involved the preparation and testing of a DP178 (SEQ ID:1) homolog for its ability to inhibit HIV-1-induced syncytia formation. As shown in FIG. 1, the sequence of DP-185 (SEQ ID:3) is slightly different from DP178 (SEQ ID:1) in that its primary sequence is taken from the HIV-1_{sf2} isolate and contains several amino acid differences relative to DP178 (SEQ ID:1) near the N terminus. As shown in FIG. 4, DP-185 (SEQ ID:3), exhibits inhibitory activity even at 312.5ng/ml, the lowest concentration tested.

20 The next series of experiments involved a comparison of DP178 (SEQ ID:1) HIV-1 and HIV-2 inhibitory activity. As shown in FIG. 5, DP178 (SEQ ID:1) blocked HIV-1-mediated syncytia formation at peptide concentrations below 1ng/ml. DP178 (SEQ ID:1) failed, however, to block HIV-2 mediated syncytia formation at concentrations as high as 10 μ g/ml. This striking 4 log selectivity of DP178 (SEQ ID:1) as an inhibitor of HIV-1-mediated cell fusion demonstrates an unexpected HIV-1 specificity in the action of DP178 (SEQ ID:1). DP178 (SEQ ID:1) inhibition of HIV-1-mediated cell fusion, but the peptide's inability to inhibit HIV-2 mediated cell fusion in the same cell

type at the concentrations tested provides further evidence for the high degree of selectivity associated with the antiviral action of DP178 (SEQ ID:1).

5 6.2.2. PEPTIDE INHIBITION OF INFECTION BY
 CELL-FREE VIRUS

DP178 (SEQ ID:1) was next tested for its ability to block CD-4⁺ CEM cell infection by cell free HIV-1 virus. The results, shown in FIG. 2, are from an experiment in which DP178 (SEQ ID:1) was assayed for its ability to block infection of CEM cells by an
10 HIV-1_{LAI} isolate. Included in the experiment were three control peptides, DP-116 (SEQ ID:9), DP-125 (SEQ ID:8), and DP-118 (SEQ ID:10). DP-116 (SEQ ID:9) represents a peptide previously shown to be inactive using this assay, and DP-125 (SEQ ID:8; Wild, C. et
15 al., 1992, Proc. Natl. Acad. Sci. USA 89:10,537) and DP-118 (SEQ ID:10) are peptides which have previously been shown to be active in this assay. Each concentration (0, 0.04, 0.4, 4, and 40 μ g/ml) of peptide was incubated with 247 TCID₅₀ units of HIV-1_{LAI}
20 virus and CEM cells. After 7 days of culture, cell-free supernatant was tested for the presence of RT activity as a measure of successful infection. The results, shown in FIG. 2, demonstrate that DP178 (SEQ ID:1) inhibited the de novo infection process mediated by the HIV-1 viral isolate at concentrations as low as
25 90ng/ml (IC₅₀=90ng/ml). In contrast, the two positive control peptides, DP-125 (SEQ ID:8) and DP-118 (SEQ ID:10), had over 60-fold higher IC₅₀ concentrations of approximately 5 μ g/ml.

In a separate experiment, the HIV-1 and HIV-2
30 inhibitory action of DP178 (SEQ ID:1) was tested with CEM cells and either HIV-1_{LAI} or HIV-2_{NIH2}. 62 TCID₅₀

HIV-1_{LAI} or 25 GCID₅₀ HIV-2_{NIH2} were used in these experiments, and were incubated for 7 days. As may be seen in FIG. 3, DP178 (SEQ ID:1) inhibited HIV-1 infection with an IC₅₀ of about 31ng/ml. In contrast, DP178 (SEQ ID:1) exhibited a much higher IC₅₀ for HIV-2_{NIH2}, thus making DP178 (SEQ ID:1) two logs more potent as a HIV-1 inhibitor than a HIV-2 inhibitor. This finding is consistent with the results of the fusion inhibition assays described, above, in Section 6.2.1, and further supports a significant level of selectivity (i.e., for HIV-1 over HIV-2).

7. EXAMPLE: THE HIV-1 INHIBITOR, DP178 (SEQ ID:1) IS NON-CYTOTOXIC

In this Example, the 36 amino acid synthetic peptide inhibitor DP178 (SEQ ID:1) is shown to be non-cytotoxic to cells in culture, even at the highest peptide concentrations (40μg/ml) tested.

7.1. MATERIALS AND METHODS

Cell proliferation and toxicity assay:

Approximately 3.8x10⁵ CEM cells for each peptide concentration were incubated for 3 days at 37°C in T25 flasks. Peptides tested were DP178 (SEQ ID:1) and DP-116 (SEQ ID:9), as described in FIG. 1. Peptides were synthesized as described, above, in Section 6.1. The concentrations of each peptide used were 0, 2.5, 10, and 40μg/ml. Cell counts were taken at incubation times of 0, 24, 48, and 72 hours.

7.2. RESULTS

Whether the potent HIV-1 inhibitor DP178 (SEQ ID:1) exhibited any cytotoxic effects was assessed by assaying the peptide's effects on the proliferation

and viability of cells in culture. CEM cells were incubated in the presence of varying concentrations of DP178 (SEQ ID:1), and DP-116 (SEQ ID:9), a peptide previously shown to be ineffective as a HIV inhibitor (Wild, C. et al., 1992, Proc. Natl. Acad. Sci. USA 89:10,537-10,541). Additionally, cells were incubated in the absence of either peptide.

The results of the cytotoxicity study demonstrate that DP178 (SEQ ID:1) exhibits no cytotoxic effects on cells in culture. As can be seen, below, in Table VI, even the proliferation and viability characteristics of cells cultured for 3 days in the presence of the highest concentration of DP178 (SEQ ID:1) tested (40µg/ml) do not significantly differ from the DP-116 (SEQ ID:9) or the no-peptide controls. The cell proliferation data is also represented in graphic form in FIG. 6. As was demonstrated in the Working Example presented above in Section 6, DP178 (SEQ ID:1) completely inhibits HIV-1 mediated syncytia formation at peptide concentrations between 1 and 10ng/ml, and completely inhibits cell-free viral infection at concentrations of at least 90ng/ml. Thus, this study demonstrates that even at peptide concentrations greater than 3 log higher than the HIV inhibitory dose, DP178 (SEQ ID:1) exhibits no cytotoxic effects.

25

30

Table VI

5	Peptide	Peptide Concentration $\mu\text{g/ml}$	% Viability at time (hours)			
			0	24	48	72
10	DP178 (SEQ ID:1)	40	98	97	95	97
		10	98	97	98	98
		2.5	98	93	96	96
15	DP116 (SEQ ID:9)	40	98	95	98	97
		10	98	95	93	98
		2.5	98	96	98	99
	No Peptide	0	98	97	99	98

20

8. EXAMPLE: THE INTERACTION OF DP178 AND DP107

Soluble recombinant forms of gp41 used in the
 example described below provide evidence that the
 DP178 peptide associates with a distal site on gp41
 whose interactive structure is influenced by the DP107
 leucine zipper motif. A single mutation disrupting
 the coiled-coil structure of the leucine zipper domain
 transformed the soluble recombinant gp41 protein from
 an inactive to an active inhibitor of HIV-1 fusion.
 This transformation may result from liberation of the
 potent DP178 domain from a molecular clasp with the

30

leucine zipper, DP107, determinant. The results also indicate that the anti-HIV activity of various gp41 derivatives (peptides and recombinant proteins) may be due to their ability to form complexes with viral gp41 and interfere with its fusogenic process.

5

8.1. MATERIALS AND METHODS

8.1.1. CONSTRUCTION OF FUSION PROTEINS AND GP41 MUTANTS

10 Construction of fusion proteins and mutants shown in FIG. 7 was accomplished as follows: the DNA sequence corresponding to the extracellular domain of gp41 (540-686) was cloned into the Xmn I site of the expression vector pMal-p2 (New England Biolab) to give M41. The gp41 sequence was amplified from pgtat
15 (Malim et al., 1988, Nature 355: 181-183) by using polymerase chain reaction (PCR) with upstream primer 5'-ATGACGCTGACGGTACAGGCC-3' (primer A) and downstream primer 5'-TGACTAAGCTTAATACCACAGCCAATTTGTTAT-3' (primer B). M41-P was constructed by using the T7-Gen
20 in vitro mutagenesis kit from United States Biochemicals (USB) following the supplier's instructions. The mutagenic primer (5'-GGAGCTGCTTGGGGCCCCAGAC-3') introduces an Ile to Pro mutation in M41 at position 578. M41Δ107, from which the DP-107 region has been deleted, was made using a
25 deletion mutagenic primer 5'-CCAAATCCCCAGGAGCTGCTCGAGCTGCACTATACCAGAC-3' (primer C) following the USB T7-Gen mutagenesis protocol. M41Δ178, from which the DP-178 region has been deleted, was made by cloning the DNA fragment
30 corresponding to gp41 amino acids 540-642 into the

Xmn I site of pMal-p2. Primer A and 5'-
ATAGCTTCTAGATTAATTGTTAATTTCTCTGTCCC-3' (primer D) were
used in the PCR with the template pgtat to generate
the inserted DNA fragments. M41-P was used as the
template with primer A and D in PCR to generate M41-
5 PA178. All inserted sequences and mutated residues
were checked by restriction enzyme analysis and
confirmed by DNA sequencing.

8.1.2. PURIFICATION AND CHARACTERIZATION OF FUSION PROTEINS

10 The fusion proteins were purified according to
the protocol described in the manufacturer's brochure
of protein fusion and purification systems from New
England Biolabs (NEB). Fusion proteins (10 ng) were
analyzed by electrophoresis on 8% SDS polyacrylamide
15 gels. Western blotting analysis was performed as
described by Sambrook et al., 1989, Molecular Cloning:
A Laboratory Manual, 2d Ed, Cold Spring Harbor
Laboratory Press, Cold Spring Harbor, NY, Ch. 18,
pp. 64-75. An HIV-1 positive serum diluted 1000-fold,
20 or a human Fab derived from repertoire cloning was
used to react with the fusion proteins. The second
antibody was HRP-conjugated goat antihuman Fab. An
ECL Western blotting detection system (Amersham) was
used to detect the bound antibody. A detailed
25 protocol for this detection system was provided by the
manufacturer. Rainbow molecular weight markers
(Amersham) were used to estimate the size of fusion
proteins.

8.1.3. CELL FUSION ASSAYS FOR ANTI-HIV ACTIVITY

30 Cell fusion assays were performed as previously
described (Matthews et al., 1987, Proc. Natl. Acad.

Sci. USA 84: 5424-5481). CEM cells (7×10^4) were incubated with HIV-1_{IIIb} chronically infected CEM cells (10^4) in 96-well flat-bottomed half-area plates (Costar) in 100 μ l culture medium. Peptide and fusion proteins at various concentrations in 10 μ l culture medium were incubated with the cell mixtures at 37°C for 24 hours. Multinucleated syncytia were estimated with microscopic examination. Both M41 and M41-P did not show cytotoxicity at the concentrations tested and shown in FIG. 8.

10 Inhibition of HIV-1 induced cell-cell fusion activity was carried out in the presence of 10 nM DP178 and various concentrations of M41 Δ 178 or M41-PA178 as indicated in FIG. 9. There was no observable syncytia in the presence of 10 nM DP178. No peptide or fusion protein was added in the control samples.

15

8.1.4. ELISA ANALYSIS OF DP178 BINDING TO THE LEUCINE ZIPPER MOTIF OF GP41

The amino acid sequence of DP178 used is:

YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF. For enzyme

20 linked immunoassay (ELISA), M41 Δ 178 or M41-PA178 (5 μ g/ml) in 0.1M NaHCO₃, pH 8.6, were coated on 96 wells Linbro ELISA plates (Flow Lab, Inc.) overnight. Each well was washed three times with distilled water then blocked with 3% bovine serum albumin (BSA) for 2 hours. After blocking, peptides with 0.5% BSA in TBST (40 mM Tris-HCl pH7.5, 150 mM NaCl, 0.05% Tween 20) were added to the ELISA plates and incubated at room temperature for 1 hour. After washing three times with TBST, Fab-d was added at a concentration of 10 ng/ml with 0.5% BSA in TBST. The plates were washed 30 three times with TBST after incubation at room temperature for 1 hour. Horse radish peroxidase (HRP)

conjugated goat antihuman Fab antiserum at a 2000 fold dilution in TBST with 0.5% BSA was added to each well and incubated at room temperature for 45 minutes. The plates were then washed four times with TBST. The peroxidase substrate o-phenylene diamine (2.5 mg/ml) and 0.15% H₂O₂ were added to develop the color. The reaction was stopped with an equal volume of 4.5 N H₂SO₄ after incubation at room temperature for 10 minutes. The optical density of the stopped reaction mixture was measured with a micro plate reader (Molecular Design) at 490 nm. Results are shown in FIG. 10.

8.2. RESULTS

8.2.1. THE EXPRESSION AND CHARACTERIZATION OF THE ECTODOMAIN OF gp41

As a step toward understanding the roles of the two helical regions in gp41 structure and function, the ectodomain of gp41 was expressed as a maltose binding fusion protein (M41) (FIG. 7). The fusogenic peptide sequence at the N-terminal of gp41 was omitted from this recombinant protein and its derivatives to improve solubility. The maltose binding protein facilitated purification of the fusion proteins under relatively mild, non-denaturing conditions. Because the M41 soluble recombinant gp41 was not glycosylated, lacked several regions of the transmembrane protein (*i.e.*, the fusion peptide, the membrane spanning, and the cytoplasmic domains), and was expressed in the absence of gp120, it was not expected to precisely reflect the structure of native gp41 on HIV-1 virions. Nevertheless, purified M41 folded in a manner that preserved certain discontinuous epitopes as evidenced by reactivity with human monoclonal antibodies, 98-6,

126-6, and 50-69, previously shown to bind conformational epitopes on native gp41 expressed in eukaryotic cells (Xu et al., 1991, J. Virol. 65: 4832-4838; Chen, 1994, J. Virol. 68:2002-2010). Thus, at least certain regions of native gp41 defined by these
5 antibodies appear to be reproduced in the recombinant fusion protein M41. Furthermore, M41 reacted with a human recombinant Fab (Fab-d) that recognizes a conformational epitope on gp41 and binds HIV-1 virions as well as HIV-1 infected cells but not uninfected
10 cells as analyzed by FACS. Deletion of either helix motif, i.e., DP107 or DP178, of the M41 fusion protein eliminated reactivity with Fab-d. These results indicate that both helical regions, separated by 60 amino acids in the primary sequence, are required to
15 maintain the Fab-d epitope.

8.2.2. ANTI-HIV ACTIVITY OF THE RECOMBINANT ECTODOMAIN OF GP41

The wild type M41 fusion protein was tested for anti-HIV-1 activity. As explained, supra, synthetic
20 peptides corresponding to the leucine zipper (DP107) and the C-terminal putative helix (DP178) show potent anti-HIV activity. Despite inclusion of both these regions, the recombinant M41 protein did not affect HIV-1 induced membrane fusion at concentrations as
25 high as 50 μ M (Table VII, below).

Table VII

**DISRUPTION OF THE LEUCINE ZIPPER OF
GP41 FREES THE ANTI-HIV MOTIF**

		<u>DP107</u>	<u>DP178</u>	<u>M41</u>	<u>M41-P</u>	<u>M41-PA178</u>
5	Cell fusion (IC ₉₀)	1 μM	1 nM >50 μM	83 nM	>50 μM	
	Fab-D binding (k _D)	-	-	3.5x10 ⁻⁹	2.5x10 ⁻⁸	-
10	HIV infectiv- ity (IC ₉₀)	1 μM	80 nM	>16 μM	66 nM	>8 μM

1 The affinity constants of Fab-d binding to the fusion proteins were determined using a protocol described by B. Friguet et al., 1985, J. Immunol. Method. 77:305-319.

15

- = No detectable binding of Fab-d to the fusion proteins.

20 *Antiviral Infectivity Assays.* 20 μl of serially diluted virus stock was incubated for 60 minutes at ambient temperature with 20 μl of the indicated concentration of purified recombinant fusion protein in RPMI 1640 containing 10% fetal bovine serum and antibiotics in a 96-well microtiter plate. 20 μl of CEM4 cells at 6 x 10⁵ cells/ml were added to each well, and cultures were incubated at 37°C in a humidified CO₂ incubator. Cells were cultured for 9 days by the addition of fresh medium every 2 to 3 days. On days 5, 7, and 9 postinfection, supernatant samples were assayed for reverse transcriptase (RT) activity, as described below, to monitor viral replication. The 50% tissue culture infectious dose (TCID₅₀) was calculated for each condition according to the formula of Reed & Muench, 1937, Am. J. Hyg. 27:493-497. RT activity was determined by a modification of the published methods of Goff et al., 1981, J. Virol. 38:239-248 and Willey et al., 1988, J. Virol. 62:139-147 as described in Chen et al., 1993, AIDS Res. Human Retroviruses 9:1079-1086.

25

30 Surprisingly, a single amino acid substitution, proline in place of isoleucine in the middle of the leucine zipper motif, yielded a fusion protein (M41-P) which did exhibit antiviral activity (Table XXV and Fig. 8). As seen in Table XXV, M41-P blocked syncytia

formation by 90% at approximately 85 nM and
neutralized HIV-1_{IIIB} infection by 90% at approximately
70 nM concentrations. The anti-HIV-1 activity of M41-
P appeared to be mediated by the C-terminal helical
sequence since deletion of that region from M41-P
5 yielded an inactive fusion protein, M41-PA178 (Table
XXV). This interpretation was reinforced by
experiments demonstrating that a truncated fusion
protein lacking the DP178 sequence, M41Δ178, abrogated
the potent anti-fusion activity of the DP178 peptide
10 in a concentration-dependent manner (FIG. 9). The
same truncated fusion protein containing the proline
mutation disrupting the leucine zipper, M41-PA178, was
not active in similar competition experiments (FIG.
9). The results indicate that the DP178 peptide
15 associates with a second site on gp41 whose
interactive structure is dependent on a wild type
leucine zipper sequence. A similar interaction may
occur within the wild type fusion protein, M41, and
act to form an intramolecular clasp which sequesters
the DP178 region, making it unavailable for anti-viral
20 activity.

A specific association between these two domains
is also indicated by other human monoclonal Fab-d
studies. For example, Fab-d failed to bind either the
DP178 peptide or the fusion protein M41Δ178, but its
25 epitope was reconstituted by simply mixing these two
reagents together (FIG. 10). Again, the proline
mutation in the leucine zipper domain of the fusion
protein, M41-PA178, failed to reconstitute the epitope
in similar mixing experiments.

30

9. EXAMPLE: METHOD FOR COMPUTER-ASSISTED
IDENTIFICATION OF DP107-LIKE
AND DP178-LIKE SEQUENCES

A number of known coiled-coil sequences have been well described in the literature and contain heptad repeat positioning for each amino acid. Coiled-coil nomenclature labels each of seven amino acids of a heptad repeat A through G, with amino acids A and D tending to be hydrophobic positions. Amino acids E and G tend to be charged. These four positions (A, D, E, and G) form the amphipathic backbone structure of a monomeric alpha-helix. The backbones of two or more amphipathic helices interact with each other to form di-, tri-, tetrameric, etc., coiled-coil structures. In order to begin to design computer search motifs, a series of well characterized coiled coils were chosen including yeast transcription factor GCN4, Influenza Virus hemagglutinin loop 36, and human proto-oncogenes c-Myc, c-Fos, and c-Jun. For each peptide sequence, a strict homology for the A and D positions, and a list of the amino acids which could be excluded for the B, C, E, F, and G positions (because they are not observed in these positions) was determined. Motifs were tailored to the DP107 and DP178 sequences by deducing the most likely possibilities for heptad positioning of the amino acids of HIV-1 Bru DP-107, which is known to have coiled-coil structure, and HIV-1 Bru DP178, which is still structurally undefined. The analysis of each of the sequences is contained in FIG. 12. For example, the motif for GCN4 was designed as follows:

1. The only amino acids (using standard single letter amino acid codes) found in the A or D positions of GCN4 were [LMNV].

2. All amino acids were found at B, C, E, F, and G positions except {CFGIMPTW}.

3. The PESEARCH motif would, therefore, be written as follows:

5 [LMNV] - {CFGIMPTW} (2) - [LMNV] - {CFGIMPTW} (3) -
 [LMNV] - {CFGIMPTW} (2) - [LMNV] - {CFGIMPTW} (3) -
 [LMNV] - {CFGIMPTW} (2) - [LMNV] - {CFGIMPTW} (3) -
 [LMNV] - {CFGIMPTW} (2) - [LMNV] - {CFGIMPTW} (3)

Translating or reading the motif: "at the first A
 10 position either L, M, N, or V must occur; at positions B and C (the next two positions) accept everything except C, F, G, I, M, P, T, or W; at the D position either L, M, N, or V must occur; at positions E, F, and G (the next 3 positions) accept everything except
 15 C, F, G, I, M, P, T, or W." This statement is contained four times in a 28-mer motif and five times in a 35-mer motif. The basic motif key then would be: [LMNV] - {CFGIMPTW}. The motif keys for the remaining well described coiled-coil sequences are summarized in FIG. 12.

20 The motif design for DP107 and DP178 was slightly different than the 28-mer model sequences described above due to the fact that heptad repeat positions are not defined and the peptides are both longer than 28 residues. FIG. 13 illustrates several possible
 25 sequence alignments for both DP107 and DP178 and also includes motif designs based on 28-mer, 35-mer, and full-length peptides. Notice that only slight differences occur in the motifs as the peptides are lengthened. Generally, lengthening the base peptide results in a less stringent motif. This is very
 30 useful in broadening the possibilities for identifying

DP107-or DP-178-like primary amino acid sequences referred to in this document as "hits".

In addition to making highly specific motifs for each type peptide sequence to be searched, it is also possible to make "hybrid" motifs. These motifs are
5 made by "crossing" two or more very stringent motifs to make a new search algorithm which will find not only both "parent" motif sequences but also any peptide sequences which have similarities to one, the other, or both "parents". For example, in FIG. 14 the
10 "parent" sequence of GCN4 is crossed with each of the possible "parent" motifs of DP-107. Now the hybrid motif must contain all of the amino acids found in the A and D positions of both parents, and exclude all of the amino acids not found in either parent at the
15 other positions. The resulting hybrid from crossing GCN4 or [LMNV]{CFGIMPTW} and DP107 (28-mer with the first L in the D position) or [ILQT]{CDFIMPST}, is [ILMNQTV]{CFIMPT}. Notice that now only two basic hybrid motifs exist which cover both framing possibilities, as well as all peptide lengths of the
20 parent DP-107 molecule. FIG. 15 represents the "hybridizations" of GCN4 with DP-178. FIG. 16 represents the "hybridizations" of DP107 and DP178. It is important to keep in mind that the represented motifs, both parent and hybrid, are motif keys and not
25 the depiction of the full-length motif needed to actually do the computer search.

Hybridizations can be performed on any combination of two or more motifs. FIG. 17 summarizes several three-motif hybridizations
30 including GCN4, DP107 (both frames), and DP178 (also both frames). Notice that the resulting motifs are now becoming much more similar to each other. In

fact, the first and third hybrid motifs are actually subsets of the second and fourth hybrid motifs respectively. This means that the first and third hybrid motifs are slightly more stringent than the second and fourth. It should also be noted that with
5 only minor changes in these four motifs, or by hybridizing them, a single motif could be obtained which would find all of the sequences. However, it should be remembered that stringency is also reduced. Finally, the most broad-spectrum and least-stringent
10 hybrid motif is described in FIG. 18 which summarizes the hybridization of GCN4, DP107 (both frames), DP178 (both frames), c-Fos, c-Jun, c-Myc, and Flu loop 36.

A special set of motifs was designed based on the fact that DP-178 is located only approximately ten
15 amino acids upstream of the transmembrane spanning region of gp41 and just C-terminal to a proline which separates DP107 and DP178. It has been postulated that DP178 may be an amphipathic helix when membrane associated, and that the proline might aid in the initiation of the helix formation. The same
20 arrangement was observed in Respiratory Syncytial Virus; however, the DP178-like region in this virus also had a leucine zipper just C-terminal to the proline. Therefore, N-terminal proline-leucine zipper motifs were designed to analyze whether any other
25 viruses might contain this same pattern. The motifs are summarized in FIG. 19.

The PC/Gene protein database contains 5879 viral amino acid sequences (library file PVIRUSES; CD-ROM release 11.0). Of these, 1092 are viral enveloped or
30 glycoprotein sequences (library file PVIRUSE1). Tables V through XIV contain lists of protein sequence

names and motif hit locations for all the motifs searched.

10. EXAMPLE: COMPUTER-ASSISTED IDENTIFICATION
OF DP107 AND DP178-LIKE SEQUENCES
IN HUMAN IMMUNODEFICIENCY VIRUS

5

FIG. 20 represents search results for HIV-1 BRU isolate gp41 (PC/Gene protein sequence PENV_HV1BR). Notice that the hybrid motif which crosses DP-107 and DP-178 (named 107x178x4; the same motif as found in FIG. 16 found three hits including amino acids 550-599, 636-688, and 796-823. These areas include DP-107 plus eight N-terminal and four C-terminal amino acids; DP178 plus seven N-terminal and ten C-terminal amino acids; and an area inside the transmembrane region (cytoplasmic). FIG. 20 also contains the results obtained from searching with the motif named ALLMOTI5, for which the key is found in FIG. 17 ({CDGHP}{CFP}x5). This motif also found three hits including DP107 (amino acids 510-599), DP178 (615-717), and a cytoplasmic region (772-841). These hits overlap the hits found by the motif 107x178x4 with considerable additional sequences on both the amino and carboxy termini. This is not surprising in that 107x178x4 is a subset of the ALLMOTI5 hybrid motif. Importantly, even though the stringency of ALLMOTI5 is considerably less than 107x178x4, it still selectively identifies the DP107 and DP178 regions of gp41 shown to contain sequences for inhibitory peptides of HIV-1. The results of these two motif searches are summarized in Table V of U.S. Patent Application Serial No. 08/470,896 filed on June 6, 1995 (incorporated herein by reference in its entirety) under the PC/Gene protein sequence name PENV_HV1BR. The proline-leucine

30

zipper motifs also gave several hits in HIV-1 BRU including 503-525 which is at the very C-terminus of gp120, just upstream of the cleavage site (P7LZIPC and P12LZIPC); and 735-768 in the cytoplasmic domain of gp41 (P23LZIPC). These results are found in Tables
 5 VIII, IX, and X under the same sequence name as mentioned above. Notice that the only area of HIV-1 BRU which is predicted by the Lupas algorithm to contain a coiled-coil region, is from amino acids 635-670. This begins eight amino acids N-terminal to the
 10 start and ends eight amino acids N-terminal to the end of DP178. DP107, despite the fact that it is a known coiled coil, is not predicted to contain a coiled-coil region using the Lupas method.

15 11. EXAMPLE: COMPUTER-ASSISTED IDENTIFICATION OF DP107-LIKE AND DP178-LIKE SEQUENCES IN HUMAN RESPIRATORY SYNCYTIAL VIRUS

FIG. 21 represents search results for Human Respiratory Syncytial Virus (RSV; Strain A2) fusion glycoprotein F1 (PC/Gene protein sequence name PVGLF_
 20 HRSVA). Motif 107x178x4 finds three hits including amino acids 152-202, 213-243, and 488-515. The arrangement of these hits is similar to what is found in HIV-1 except that the motif finds two regions with similarities to DP-178, one just downstream of what
 25 would be called the DP107 region or amino acids 213-243, and one just upstream of the transmembrane region (also similar to DP178) or amino acids 488-515. Motif ALLMOTIS also finds three areas including amino acids 116-202, 267-302, and 506-549. The proline-leucine
 30 zipper motifs also gave several hits including amino acids 205-221 and 265-287 (P1LZIPC 265-280, P12LZIPC),

and 484-513 (P7LZIPC and P12LZIPC 484-506, P23LZIPC). Notice that the PLZIP motifs also identify regions which share location similarities with DP-178 of HIV-1.

5 12. EXAMPLE: COMPUTER-ASSISTED IDENTIFICATION OF
DP107-LIKE AND DP178-LIKE SEQUENCES
IN SIMIAN IMMUNODEFICIENCY VIRUS

Motif hits for Simian immunodeficiency Virus gp41 (AGM3 isolate; PC/Gene protein sequence name
PENV_SIVAG) are shown in FIG. 22. Motif 107x178x4
10 finds three hits including amino acids 566-593, 597-624, and 703-730. The first two hits only have three amino acids between them and could probably be combined into one hit from 566-624 which would represent a DP107-like hit. Amino acids 703 to 730
15 would then represent a DP178-like hit. ALLMOTI5 also finds three hits including amino acids 556-628 (DP107-like), 651-699 (DP178-like), and 808-852 which represents the transmembrane spanning region. SIV also has one region from 655-692 with a high
20 propensity to form a coiled coil as predicted by the Lupas algorithm. Both 107x178x4 and ALLMOTI5 motifs find the same region. SIV does not have any PLZIP motif hits in gp41.

The identification of DP178/DP107 analogs for a
25 second SIV isolate (MM251) is demonstrated in the Example presented, below, in Section 19.

13. EXAMPLE: COMPUTER-ASSISTED IDENTIFICATION OF
DP107-LIKE AND DP178 LIKE SEQUENCES
IN CANINE DISTEMPER VIRUS

30 Canine Distemper Virus (strain Onderstepoort)
fusion glycoprotein F1 (PC/Gene Protein sequence name

PVGLF_CDVO) has regions similar to Human RSV which are predicted to be DP107-like and DP178-like (FIG. 23). Motif 107x178x4 highlights one area just C-terminal to the fusion peptide at amino acids 252-293. Amino acids 252-286 are also predicted to be coiled coil using the Lupas algorithm. Almost 100 amino acids C-terminal to the first region is a DP178-like area at residues 340-367. ALLMOTI5 highlights three areas of interest including: amino acids 228-297, which completely overlaps both the Lupas prediction and the DP107-like 107x178x4 hit; residues 340-381, which overlaps the second 107x178x4 hit; and amino acids 568-602, which is DP178-like in that it is located just N-terminal to the transmembrane region. It also overlaps another region (residues 570-602) predicted by the Lupas method to have a high propensity to form a coiled coil. Several PLZIP motifs successfully identified areas of interest including P6 and P12LZIPC which highlight residues 336-357 and 336-361 respectively; P1 and P12LZIPC which find residues 398-414; and P12 and P23LZIPC which find residues 562-589 and 562-592 respectively.

14. EXAMPLE: COMPUTER-ASSISTED IDENTIFICATION OF
DP107-LIKE AND DP178-LIKE SEQUENCES
IN NEWCASTLE DISEASE VIRUS

FIG. 24 shows the motif hits found in Newcastle Disease Virus (strain Australia-Victoria/32; PC Gene protein sequence name PVGLF_NDVA). Motif 107x178x4 finds two areas including a DP107-like hit at amino acids 151-178 and a DP178-like hit at residues 426-512. ALLMOTI5 finds three areas including residues 117-182, 231-272, and 426-512. The hits from 426-512 include a region which is predicted by the Lupas

method to have a high coiled-coil propensity (460-503). The PLZIP motifs identify only one region of interest at amino acids 273-289 (P1 and 12LZIPC).

5 15. EXAMPLE: COMPUTER-ASSISTED IDENTIFICATION
OF DP107-LIKE AND DP178-LIKE
SEQUENCES IN HUMAN PARAINFLUENZA VIRUS

Both motifs 107x178x4 and ALLMOTI5 exhibit DP107-like hits in the same region, 115-182 and 117-182 respectively, of Human Parainfluenza Virus (strain NIH 47885; PC/Gene protein sequence name PVGLF_p13H4; 10 (FIG. 25). In addition, the two motifs have a DP178-like hit just slightly C-terminal at amino acids 207-241. Both motifs also have DP178-like hits nearer the transmembrane region including amino acids 457-497 and 462-512 respectively. Several PLZIP motif hits are 15 also observed including 283-303 (P5LZIPC), 283-310 (P12LZIPC), 453-474 (P6LZIPC), and 453-481 (P23LZIPC). The Lupas algorithm predicts that amino acids 122-176 may have a propensity to form a coiled-coil.

20 16. EXAMPLE: COMPUTER-ASSISTED IDENTIFICATION OF
DP107-LIKE AND DP178-LIKE SEQUENCES OF
INFLUENZA A VIRUS

FIG. 26 illustrates the Lupas prediction for a coiled coil in Influenza A Virus (strain A/Aichi/2/68) at residues 379-436, as well as the motif hits for 25 107x178x4 at amino acids 387-453, and for ALLMOTI5 at residues 380-456. Residues 383-471 (38-125 of HA2) were shown by Carr and Kim to be an extended coiled coil when under acidic pH (Carr and Kim, 1993, Cell 73: 823-832). The Lupas algorithm predicts a coiled- 30 coil at residues 379-436. All three methods successfully predicted the region shown to actually

have coiled-coil structure; however, ALLMOTI5 predicted the greatest portion of the 88 residue stretch.

5 17. EXAMPLE: POTENTIAL RESPIRATORY SYNCYTIAL VIRUS
DP178/DP107 ANALOGS: CD AND
ANTIVIRAL CHARACTERIZATION

10 In the Example presented herein, respiratory syncytial virus (RSV) peptides identified by utilizing the computer-assisted search motifs described in the Examples presented in Sections 9 and 11, above, were
15 tested for anti-RSV activity. Additionally, circular dichroism (CD) structural analyses were conducted on the peptides, as discussed below. It is demonstrated that several of the identified peptides exhibit potent antiviral capability. Additionally, it is shown that
several of these peptides exhibit a substantial helical character.

17.1 MATERIALS AND METHODS

20 Structural analyses: The CD spectra were measured in a 10mM sodium phosphate, 150mM sodium chloride, pH 7.0, buffer at approximately 10mM concentrations, using a 1 cm pathlength cell on a Jobin/Yvon Autodichrograph Mark V CD
spectrophotometer. Peptides were synthesized according to the methods described, above, in Section
25 6.1. Peptide concentrations were determined from A_{280} using Edlehoch's method (1967, Biochemistry 6:1948).

Anti-RSV antiviral activity assays: The assay utilized herein tested the ability of the peptides to disrupt the ability of HEp2 cells acutely infected
30 with RSV (i.e., cells which are infected with a multiplicity of infection of greater than 2) to fuse

and cause syncytial formation on a monolayer of uninfected an uninfected line of Hep-2 cells. The lower the observed level of fusion, the greater the antiviral activity of the peptide was determined to be.

5 Uninfected confluent monolayers of Hep-2 cells were grown in microtiter wells in 3% EMEM (Eagle Minimum Essential Medium w/o L-glutamine [Bio Whittaker Cat. No. 12-125F], with fetal bovine serum [FBS; which had been heat inactivated for 30 minutes
10 at 56°C; Bio Whittaker Cat. No. 14-501F) supplemented at 3%, antibiotics (penicillin/streptomycin; Bio Whittaker Cat. No. 17-602E) added at 1%, and glutamine added at 1%.

 To prepare Hep2 cells for addition to uninfected
15 cells, cultures of acutely infected Hep2 cells were washed with DPBS (Dulbecco's Phosphate Buffered Saline w/o calcium or magnesium; Bio Whittaker Cat. No. 17-512F) and cell monolayers were removed with Versene (1:5000; Gibco Life Technologies Cat. No. 15040-017). The cells were spun 10 minutes and resuspended in 3%
20 FBS. Cell counts were performed using a hemacytometer. Persistent cells were added to the uninfected Hep-2 cells.

 The antiviral assay was conducted by, first, removing all media from the wells containing
25 uninfected Hep-2 cells, then adding peptides (at the dilutions described below) in 3% EMEM, and 100 acutely RSV-infected Hep2 cells per well. Wells were then incubated at 37°C for 48 hours.

 After incubation, cells in control wells were
30 checked for fusion centers, media was removed from the wells, followed by addition, to each well, of either Crystal Violet stain or XTT. With respect to Crystal

Violet, approximately 50 μ l 0.25% Crystal Violet stain in methanol were added to each well. The wells were rinsed immediately, to remove excess stain, and were allowed to dry. The number of syncytia per well were then counted, using a dissecting microscope.

5 With respect to XTT (2,3-bis[2-Methoxy-4-nitro-5-sulfophenyl]-2H-tetrazolium-5-carboxyanilide inner salt), 50 μ l XTT (1mg/ml in RPMI buffered with 100mM HEPES, pH 7.2-7.4, plus 5% DMSO) were added to each well. The OD_{450/690} was measured (after blanking against
10 growth medium without cells or reagents, and against reagents) according to standard procedures.

Peptides: The peptides characterized in the study presented herein were:

- 1) peptides T-142 to T-155 and T-575, as shown in FIG. 27A, and peptides T-22 to T-27, T-68, T-334 and T-371
15 to T-375 and T-575, as shown in FIG. 27B;
- 2) peptides T-120 to T-141 and T-576, as shown in FIG. 27B, and peptides T-12, T-13, T-15, T-19, T-28 to T-30, T-66, T-69, T-70 and T-576, as shown in FIG. 27D; and
- 20 3) peptides T-67 and T-104 to T-119 and T-384, as shown in FIG. 28A, and peptides T-71, T-613 to T-617, T-662 to T-676 and T-730, as shown in FIG. 28B.

The peptides of group 1 represent portions of the RSV F2 protein DP178/107-like region. The peptides of
25 group 2 represent portions of the RSV F1 protein DP107-like region. The peptides of groups 3 represent portions of the RSV F1 protein DP178-like region.

Each peptide was tested at 2-fold serial dilutions ranging from 100 μ g/ml to approximately
30 100ng/ml. For each of the assays, a well containing no peptide was also used. The IC₅₀ data for each

peptide represents the average of several experiments conducted utilizing that peptide.

17.2 RESULTS

5 The data summarized in FIGS. 27A-B and 28A-B represent antiviral and structural information obtained from peptides derived from the RSV F2 DP178/DP107-like F2 region (FIG. 27A-B), the RSV F1 DP-107-like region (FIG. 27C-D) and the RSV DP178-like F2 region (FIG. 28A-B).

10 As shown in FIGS. 27A-D, a number of the RSV DP178/DP107-like peptides exhibited a detectable level of antiviral activity. Peptides from the RSV DP178/DP107-like F2 region (FIG. 27A-B), for example, T-142 to T-145 and T-334 purified peptides, exhibited
15 detectable levels of antiviral activity, as evidenced by their IC_{50} values. Further, a number of RSV F1 DP107-like peptides (FIG. 27C-D) exhibited a sizable level of antiviral activity as purified peptides, including, for example, peptides T-124 to T-127, T-131, T-135 and T-137 to T-139, as demonstrated by
20 their low IC_{50} values. In addition, CD analysis FIG. 27A, 27C) reveals that many of the peptides exhibit some detectable level of helical structure.

The results summarized in FIG. 28A-B demonstrate that a number of DP178-like purified peptides exhibit
25 a range of potent anti-viral activity. These peptides include, for example, T-67, T-104, T-105 and T-107 to T-119, as listed in FIG. 28A, and T-665 to T-669 and T-671 to T-673, as listed in FIG. 28B. In addition, some of the DP178-like peptides exhibited some level
30 of helicity.

Thus, the computer assisted searches described, hereinabove, successfully identified viral peptide

domains that represent highly promising anti-RSV antiviral compounds.

18. EXAMPLE: POTENTIAL HUMAN PARAINFLUENZA VIRUS
TYPE 3 DP178/DP107 ANALOGS: CD AND
ANTIVIRAL CHARACTERIZATION

5

In the Example presented herein, human parainfluenza virus type 3 (HPIV3) peptides identified by utilizing the computer-assisted search motifs described in the Examples presented in Sections 9 and 15, above, were tested for anti-HPIV3 activity. 10 Additionally, circular dichroism (CD) structural analyses were conducted on the peptides, as discussed below. It is demonstrated that several of the identified peptides exhibit potent antiviral capability. Additionally, it is shown that several of 15 these peptides exhibit a substantial helical character.

18.1 MATERIALS AND METHODS

Structural analyses: Structural analyses 20 consisted of circular dichroism (CD) studies. The CD spectra were measured in a 10mM sodium phosphate, 150mM sodium chloride, pH 7.0, buffer at approximately 10mM concentrations, using a 1 cm pathlength cell on a Jobin/Yvon Autodichrograph Mark V CD 25 spectrophotometer. Peptide concentrations were determined from A_{280} using Edlehoch's method (1967, Biochemistry 6:1948).

Anti-HPIV3 antiviral activity assays: The assay 30 utilized herein tested the ability of the peptides to disrupt the ability of Hep2 cells chronically infected with HPIV3 to fuse and cause syncytial formation on a monolayer of an uninfected line of CV-1W cells. The

more potent the lower the observed level of fusion,
the greater the antiviral activity of the peptide.

Uninfected confluent monolayers of CV-1W cells
were grown in microtiter wells in 3% EMEM (Eagle
Minimum Essential Medium w/o L-glutamine [Bio
5 Whittaker Cat. No. 12-125F], with fetal bovine serum
[FBS; which had been heat inactivated for 30 minutes
at 56°C; Bio Whittaker Cat. No. 14-501F) supplemented
at 3%, antibiotics/antimycotics (Gibco BRL Life
Technologies Cat. No. 15040-017) added at 1%, and
10 glutamine added at 1%.

To prepare Hep2 cells for addition to uninfected
cells, cultures of chronically infected Hep2 cells
were washed with DPBS (Dulbecco's Phosphate Buffered
Saline w/o calcium or magnesium; Bio Whittaker Cat.
15 No. 17-512F) and cell monolayers were removed with
Versene (1:5000; Gibco Life Technologies Cat. No.
15040-017). The cells were spun 10 minutes and
resuspended in 3% FBS. Cell counts were performed
using a hemacytometer. Persistent cells were added to
the uninfected CV-1W cells.

20 The antiviral assay was conducted by, first,
removing all media from the wells containing
uninfected CV-1W cells, then adding peptides (at the
dilutions described below) in 3% EMEM, and 500
chronically HPIV3-infected Hep2 cells per well. Wells
25 were then incubated at 37°C for 24 hours.

On day 2, after cells in control wells were
checked for fusion centers, media was removed from the
wells, followed by addition, to each well, of
approximately 50µl 0.25% Crystal Violet stain in
30 methanol. Wells were rinsed immediately, to remove
excess stain and were then allowed to dry. The number

of syncytia per well were then counted, using a dissecting microscope.

Alternatively, instead of Crystal Violet analysis, cells were assayed with XTT, as described, above, in Section 17.1.

5 Peptides: The peptides characterized in the study presented herein were:

- 1) Peptides 157 to 188, as shown in FIG. 29A, and peptides T-38 to T-40, T-42 to T-46 and T-582, as shown in FIG. 29B. These peptides are derived from the DP107 region of the HPIV3 F1 fusion protein (represented by HPF3 107, as shown in FIG. 29A); and
- 10 2) Peptides 189 to 210, as shown in FIG. 30A, and T-269, T-626, T-383 and T-577 to T-579, as shown in FIG. 30B. These peptides are primarily derived from the DP178 region of the HPIV3 F1 fusion protein (represented by HPF3 178, as shown in FIG. 30A). Peptide T-626 contains two mutated amino acid residues (represented by a shaded background). Additionally, peptide T-577
15 represents F1 amino acids 65-100, T-578 represents F1 amino acids 207-242 and T-579 represents F1 amino acids 273-309.
20

Each peptide was tested at 2-fold serial
25 dilutions ranging from 500 μ g/ml to approximately 500ng/ml. For each of the assays, a well containing no peptide was also used.

18.2 RESULTS

30 The data summarized in FIGS. 29A-C and 30A-B represent antiviral and structural information obtained from peptides derived from the HPIV3 fusion

protein DP107-like region (FIG. 29A-C) and the HPIV3 fusion protein DP178-like region (FIG. 30A-B).

As shown in FIG. 29A-B, a number of the HPIV3 DP107-like peptides exhibited potent levels of antiviral activity. These peptides include, for
5 example, peptides T-40, T-172 to T-175, T-178, T-184 and T-185.

CD analysis reveals that a number of the peptides exhibit detectable to substantial level of helical structure. The CD spectra for one of the peptides,
10 184, which exhibits substantial helicity is summarized in FIG. 29C.

The results summarized in FIG. 30A-B demonstrate that a number of the DP178-like peptides tested exhibit a range of anti-viral activity. These
15 peptides include, for example, peptides 194 to 211, as evidenced by their low IC_{50} values. In fact, peptides 201 to 205 exhibit IC_{50} values in the nanogram/ml range. In addition, many of the DP178-like peptides exhibited some level of helicity.

Thus, the computer assisted searches described,
20 hereinabove, have successfully identified viral peptide domains that represent highly promising anti-HPIV3 antiviral compounds.

19. EXAMPLE: COMPUTER-ASSISTED IDENTIFICATION OF
25 DP178/DP107 ANALOGS IN SIMIAN
IMMUNODEFICIENCY VIRUS

FIG. 31 represents search results for SIV isolate MM251 (PC/Gene® protein sequence PENV_SIVM2). Both 107x178x4 and ALLMOTI5 search motifs identified two regions with similarities to DP107 and/or DP178.

30 The peptide regions found by 107x178x4 were located at amino acid residues 156-215 and 277-289.

The peptide regions found by ALLMOTI5 were located at amino acid residues 156-219 and 245-286. Both motifs, therefore, identify similar regions.

Interestingly, the first SIV peptide region (i.e., from amino acid residue 156 to approximately
5 amino acid residue 219) correlates with a DP107 region, while the second region identified (i.e., from approximately amino acid residue 245 to approximately amino acid residue 289) correlates with the DP178 region of HIV. In fact, an alignment of SIV isolate
10 MM251 and HIV isolate BRU, followed by a selection of the best peptide matches for HIV DP107 and DP178, reveals that the best matches are found within the peptide regions identified by the 107x178x4 and ALLMOTI5 search motifs.

It should be noted that a potential coiled-coil
15 region at amino acid residues 242-282 is predicted by the Lupas program. This is similar to the observation in HIV in which the coiled-coil is predicted by the Lupas program to be in the DP178 rather than in the DP107 region. It is possible, therefore, that SIV may
20 be similar to HIV in that it may contain a coiled-coil structure in the DP107 region, despite such a structure being missed by the Lupas algorithm. Likewise, it may be that the region corresponding to a DP178 analog in SIV may exhibit an undefined
25 structure, despite the Lupas program's prediction of a coiled-coil structure.

20. EXAMPLE: COMPUTER-ASSISTED IDENTIFICATION OF
DP178/DP107 ANALOGS IN EPSTEIN-BARR
VIRUS

30 The results presented herein describe the identification of DP178/DP107 analogs within two

different Epstein-Barr Virus proteins. Epstein-Barr is a human herpes virus which is the causative agent of, for example, infectious mononucleosis (IM), and is also associated with nasopharyngeal carcinomas (NPC), Burkitt's lymphoma and other diseases. The virus
5 predominantly exists in the latent form and is activated by a variety of stimuli.

FIG. 32 depicts the search motif results for the Epstein-Barr Virus (Strain B95-8; PC/Gene® protein sequence PVGLB_EBV) glycoprotein gp110 precursor
10 (gp115). The 107x178x4 motif identified two regions of interest, namely the regions covered by amino acid residues 95-122 and 631-658. One PZIP region was identified at amino acid residue 732-752 which is most likely a cytoplasmic region of the protein. The Lupas
15 algorithm predicts a coiled-coil structure for amino acids 657-684. No ALLMOTI5 regions were identified.

FIG. 33 depicts the search motif results for the Zebra (or EB1) trans-activator protein (BZLF1) of the above-identified Epstein-Barr virus. This protein is a transcription factor which represents the primary
20 mediator of viral reactivation. It is a member of the b-ZIP family of transcription factors and shares significant homology with the basic DNA-binding and dimerization domains of the cellular oncogenes c-fos and C/EBP. The Zebra protein functions as a
25 homodimer.

Search results demonstrate that the Zebra protein exhibits a single region which is predicted to be either of DP107 or DP178 similarity, and is found between the known DNA binding and dimerization regions
30 of the protein. Specifically, this region is located at amino acid residues 193-220, as shown in FIG. 33. The Lupas program predicted no coiled-coil regions.

21. EXAMPLE: COMPUTER-ASSISTED IDENTIFICATION OF
DP178/DP107 ANALOGS IN MEASLES VIRUS

FIG. 34 illustrates the motif search results for the fusion protein F1 of measles virus, strain Edmonston (PC Gene® protein sequence PVGLF_MEASE),
5 successfully identifying DP178/DP107 analogs.

The 107x178x4 motif identifies a single region at amino acid residues 228-262. The ALLMOTI5 search motif identifies three regions, including amino acid residues 116-184, 228-269 and 452-500. Three regions
10 containing proline residues followed by a leucine zipper-like sequence were found beginning at proline residues 214, 286 and 451.

The Lupas program identified two regions it predicted had potential for coiled-coil structure, which include amino acid residues 141-172 and 444-483.
15

22. EXAMPLE: COMPUTER-ASSISTED IDENTIFICATION OF
DP178/DP107 ANALOGS IN HEPATITIS B
VIRUS

FIG. 35 depicts the results of a PZIP motif search conducted on the Hepatitis B virus subtype AYW.
20 Two regions of interest within the major surface antigen precursor S protein were identified. The first lies just C-terminal to the proposed fusion peptide of the major surface antigen (Hbs) which is found at amino acid residues 174-191. The second
25 region is located at amino acid residues 233-267. The Lupas program predicts no coiled-coil repeat regions.

In order to test the potential anti-HBV antiviral activity of these D178/DP107 analog regions, peptides derived from area around the analog regions are
30 synthesized, as shown in FIG. 52A-B. These peptides represent one amino acid peptide "walks" through the putative DP178/DP107 analog regions. The peptides are

synthesized according to standard Fmoc chemistry on Rinkamide MBHA resins to provide for carboxy terminal blockade (Chang, C.D. and Meinhofer, J., 1978, Int. J. Pept. Protein Res. 11:246-249; Fields, G.B. and Noble, R.L., 1990, Int. J. Pept. Protein Res. 35:161-214).

- 5 Following complete synthesis, the peptide amino-terminus is blocked through automated acetylation and the peptide is cleaved with trifluoroacetic acid (TFA) and the appropriate scavengers (King, D.S. et al., 1990, Int. J. Pept. Res. 36:255-266). After cleavage,
10 the peptide is precipitated with ether and dried under vacuum for 24 hours.

- The anti-HBV activity of the peptides is tested by utilizing standard assays to determine the test peptide concentration required to cause an acceptable
15 (e.g., 90%) decrease in the amount of viral progeny formed by cells exposed to an HBV viral inoculum. Candidate antiviral peptides are further characterized in model systems such as wood chuck tissue culture and animal systems, prior to testing on humans.

- 20 23. EXAMPLE: COMPUTER-ASSISTED IDENTIFICATION OF DP178/DP107 ANALOGS IN SIMIAN MASON-PFIZER MONKEY VIRUS

- The results depicted herein illustrate the results of search motifs conducted on the Simian Mason-Pfizer monkey virus. The motifs reveal
25 DP178/DP107 analogs within the enveloped (TM) protein GP20, as shown in FIG. 36.

- The 107x178x4 motifs identifies a region at amino acid residues 422-470. The ALLMOTIS finds a region at amino acid residues 408-474. The Lupas program
30 predicted a coiled-coil structure a amino acids 424-459.

24. EXAMPLE: COMPUTER-ASSISTED IDENTIFICATION OF
DP178/DP107 ANALOGS IN BACTERIAL
PROTEINS

The results presented herein demonstrate the identification of DP178/DP107 analogs corresponding to sequences present in proteins of a variety of
5 bacterial species.

FIG. 37 depicts the search motif results for the *Pseudomonas aeruginosa* fimbrial protein (Pilin). Two regions were identified by motifs 107x178x4 and ALLMOTI5. The regions located at amino acid residues
10 30-67 and 80-144 were identified by the 107x178x4 motif. The regions at amino acid residues 30-68 and 80-125 were identified by the ALLMOTI5.

FIG. 38 depicts the search motif results for the *Pseudomonas gonorrhoeae* fimbrial protein (Pilin). A
15 single region was identified by both the 107x178x4 and the ALLMOTI5 motifs. The region located at amino acid residues 66-97 was identified by the 107x178x4 motif. The region located at amino acid residues 66-125 were identified by the ALLMOTI5 search motif. No coiled-coil regions were predicted by the Lupas program.
20

FIG. 39 depicts the search motif results for the *Hemophilus Influenza* fimbrial protein (Pilin). A single region was identified by both the 107x178x4 and the ALLMOTI5 motifs. The region located at amino acid residues 102-129 was identified by the 107x178x4
25 motif. The region located at amino acid residues 102-148 were identified by the ALLMOTI5 search motif. No coiled-coil regions were predicted by the Lupas program.

FIG. 40 depicts the search motif results for the
30 *Staphylococcus aureus* toxic shock syndrome *Hemophilus Influenza* fimbrial protein (Pilin). A single region

was identified by both the 107x178x4 and the ALLMOTI5 motifs. The region located at amino acid residues 102-129 was identified by the 107x178x4 motif. The region located at amino acid residues 102-148 were identified by the ALLMOTI5 search motif. No coiled-coil regions were predicted by the Lupas program.

FIG. 41 summarizes the motif search results conducted on the Staphylococcus aureus enterotoxin Type E protein. These results demonstrate the successful identification of DP178/DP107 analogs corresponding to peptide sequences within this protein, as described below.

The ALLMOTI5 motif identified a region at amino acid residues 22-27. The 107x178x4 motif identified two regions, with the first at amino acid residues 26-69 and the second at 88-115. A P12LZIPC motif search identified two regions, at amino acid residues 163-181 and 230-250.

The Lupas program predicted a region with a high propensity for coiling at amino acid residues 25-54. This sequence is completely contained within the first region identified by both ALLMOTI5 and 107x178x4 motifs.

FIG. 42 depicts the search motif results conducted on a second Staphylococcus aureus toxin, enterotoxin A. Two regions were identified by the ALLMOTI5 motif, at amino acid residues 22-70 and amino acid residues 164-205. The 107x178x4 motif found two regions, the first at amino acid residues 26-69 and the second at amino acid residues 165-192. A P23LZIPC motif search revealed a region at amino acid residues 216-250. No coiled-coil regions were predicted by the Lupas program.

FIG. 43 shows the motif search results conducted on the E. coli heat labile enterotoxin A protein, demonstrating that identification of DP178/DP107 analogs corresponding to peptides located within this protein. Two regions were identified by the ALLMOTI5 motif, with the first residing at amino acid residues 55-115, and the second residing at amino acid residues 216-254. The 107x178x4 motif identified a single region at amino acid residues 78-105. No coiled-coil regions were predicted by the Lupas program.

10

25. EXAMPLE: COMPUTER-ASSISTED IDENTIFICATION OF
DP178/DP107 ANALOGS WITHIN VARIOUS
HUMAN PROTEINS

The results presented herein demonstrate the identification of DP178/DP107 analogs corresponding to peptide sequences present within several different human proteins.

FIG. 44 illustrates the search motif results conducted on the human c-fos oncoprotein. The ALLMOTI5 motif identified a single region at amino acid residues 155-193. The 107x178x4 motif identified one region at amino acid residues 162-193. The Lupas program predicted a region at amino acid residues 148-201 to have coiled-coil structure.

FIG. 45 illustrates the search motif results conducted on the human lupus KU autoantigen protein P70. The ALLMOTI5 motif identified a single region at amino acid residues 229-280. The 107x178x4 motif identified one region at amino acid residues 235-292. The Lupas program predicted a region at amino acid residues 232-267 to have coiled-coil structure.

FIG. 46 illustrates the search motif results conducted on the human zinc finger protein 10. The

ALLMOTI5 motif identified a single region at amino acid residues 29-81. The 107x178x4 motif identified one region at amino acid residues 29-56. A P23LZIPC motif search found a single region at amino acid residues 420-457. The Lupas program predicted no
5 coiled-coil regions.

26. EXAMPLE: POTENTIAL MEASLES VIRUS DP178/DP107
ANALOGS: CD AND ANTIVIRAL
CHARACTERIZATION

In the Example presented herein, measles (MeV)
10 virus DP178-like peptides identified by utilizing the computer-assisted search motifs described in the Examples presented in Sections 9 and 21, above, are tested for anti-MeV activity. Additionally, circular dichroism (CD) structural analyses are conducted on
15 the peptides, as discussed below. It is demonstrated that several of the identified peptides exhibit potent antiviral capability. Additionally, it is shown that none of the these peptides exhibit a substantial helical character.

20

26.1 MATERIALS AND METHODS

Structural analyses: The CD spectra were measured in a 10mM sodium phosphate, 150mM sodium chloride, pH 7.0, buffer at approximately 10mM concentrations, using a 1 cm pathlength cell on a
25 Jobin/Yvon Autodichrograph Mark V CD spectrophotometer. Peptide concentrations were determined from A_{280} using Edlehoch's method (1967, Biochemistry 6:1948).

Anti-MeV antiviral activity syncytial reduction
30 assay: The assay utilized herein tested the ability of the peptides to disrupt the ability of Vero cells

acutely infected with MeV (i.e., cells which are infected with a multiplicity of infection of 2-3) to fuse and cause syncytial formation on a monolayer of an uninfected line of Vero cells. The more potent the peptide, the lower the observed level of fusion, the greater the antiviral activity of the peptide.

Uninfected confluent monolayers of Vero cells were grown in microtiter wells in 10% FBS EMEM (Eagle Minimum Essential Medium w/o L-glutamine [Bio Whittaker Cat. No. 12-125F], with fetal bovine serum [FBS; which had been heat inactivated for 30 minutes at 56°C; Bio Whittaker Cat. No. 14-501F) supplemented at 10%, antibiotics/antimycotics (Bio Whittaker Cat. No. 17-602E) added at 1%, and glutamine added at 1%.

To prepare acutely infected Vero cells for addition to the uninfected cells, cultures of acutely infected Vero cells were washed twice with HBSS (Bio Whittaker Cat. No. 10-543F) and cell monolayers were removed with trypsin (Bio Whittaker Cat. No. 17-161E). Once cells detached, media was added, any remaining clumps of cells were dispersed, and hemacytometer cell counts were performed.

The antiviral assay was conducted by, first, removing all media from the wells containing uninfected Vero cells, then adding peptides (at the dilutions described below) in 10% FBS EMEM, and 50-100 acutely MeV-infected Vero cells per well. Wells were then incubated at 37°C for a maximum of 18 hours.

On day 2, after cells in control wells were checked for fusion centers, media was removed from the wells, followed by addition, to each well, of approximately 50 μ l 0.25% Crystal Violet stain in methanol. Wells were rinsed twice with water immediately, to remove excess stain and were then

allowed to dry. The number of syncytia per well were then counted, using a dissecting microscope.

Anti-MeV antiviral activity plaque reduction assay: The assay utilized herein tested the ability of the peptides to disrupt the ability of MeV to
5 infect permissive, uninfected Vero cells, leading to the infected cells' fusing with uninfected cells to produce syncytia. The lower the observed level of syncytial formation, the greater the antiviral activity of the peptide.

10 Monolayers of uninfected Vero cells are grown as described above.

The antiviral assay was conducted by, first, removing all media from the wells containing uninfected Vero cells, then adding peptides (at the
15 dilutions described below) in 10% FBS EMEM, and MeV stock virus at a final concentration of 30 plaque forming units (PFU) per well. Wells were then incubated at 37°C for a minimum of 36 hours and a maximum of 48 hours.

On day 2, after cells in control wells were
20 checked for fusion centers, media was removed from the wells, followed by addition, to each well, of approximately 50 μ l 0.25% Crystal Violet stain in methanol. Wells were rinsed twice with water immediately, to remove excess stain and were then
25 allowed to dry. The number of syncytia per well were then counted, using a dissecting microscope.

Peptides: The peptides characterized in the study presented herein were peptides T-252A0 to T-256A0, T-257B1/C1, and T-258B1 to T-265B0, and T-266A0
30 to T-268A0, as shown in FIG. 47. These peptides represent a walk through the DP178-like region of the MeV fusion protein.

Each peptide was tested at 2-fold serial dilutions ranging from 100 μ g/ml to approximately 100ng/ml. For each of the assays, a well containing no peptide was also used.

5

26.2 RESULTS

The data summarized in FIG. 47 represents antiviral and structural information obtained via "peptide walks" through the DP178-like region of the MeV fusion protein.

10

As shown in FIG. 47, the MeV DP178-like peptides exhibited a range of antiviral activity as crude peptides. Several of these peptides were chosen for purification and further antiviral characterization. The IC₅₀ values for such peptides were determined, as shown in FIG. 47, and ranged from 1.35 μ g/ml (T-257B1/C1) to 0.072 μ g/ml (T-265B1). None of the DP178-like peptides showed, by CD analysis, a detectable level of helicity.

15

20

Thus, the computer assisted searches described, hereinabove, as in for example, the Example presented in Section 9, for example, successfully identified viral peptide domains that represent highly promising anti-MeV antiviral compounds.

27. EXAMPLE: POTENTIAL SIV DP178/DP107 ANALOGS: ANTIVIRAL CHARACTERIZATION

25

In the Example presented herein, simian immunodeficiency virus (SIV) DP178-like peptides identified by utilizing the computer-assisted search motifs described in the Examples presented in Sections 9, 12 and 19, above, were tested for anti-SIV activity. It is demonstrated that several of the

30

identified peptides exhibit potent antiviral capability.

27.1 MATERIALS AND METHODS

5 Anti-SIV antiviral assays: The assay utilized herein were as reported in Langolis et al. (Langolis, A.J. et al., 1991, AIDS Research and Human Retroviruses 7:713-720).

10 Peptides: The peptides characterized in the study presented herein were peptides T-391 to T-400, as shown in FIG. 48. These peptides represent a walk through the DP178-like region of the SIV TM protein.

15 Each peptide was tested at 2-fold serial dilutions ranging from 100µg/ml to approximately 100ng/ml. For each of the assays, a well containing no peptide was also used.

27.2 RESULTS

The data summarized in FIG. 48 represents antiviral information obtained via "peptide walks" through the DP178-like region of the SIV TM protein.

20 As shown in FIG. 48, peptides T-391 to T-400 were tested and exhibited a potent antiviral activity as crude peptides.

25 Thus, the computer assisted searches described, hereinabove, as in for example, the Example presented in Section 9, for example, successfully identified viral peptide domains that represent highly promising anti-SIV antiviral compounds.

28. EXAMPLE: ANTI-VIRAL ACTIVITY OF DP107 AND DP-178 PEPTIDE TRUNCATIONS AND MUTATIONS

30 The Example presented in this Section represents a study of the antiviral activity of DP107 and DP178

truncations and mutations. It is demonstrated that several of these DP107 and DP178 modified peptides exhibit substantial antiviral activity.

28.1 MATERIALS AND METHODS

5 Anti-HIV assays: The antiviral assays performed were as those described, above, in Section 6.1. Assays utilized HIV-1/IIIb and/or HIV-2 NIH2 isolates. Purified peptides were used, unless otherwise noted in FIGS. 49A-C.

10 Peptides: The peptides characterized in the study presented herein were:

1) FIGS. 49A-C present peptides derived from the region around and containing the DP178 region of the HIV-1 BRU isolate.

15 Specifically, this region spanned from gp41 amino acid residue 615 to amino acid residue 717. The peptides listed contain truncations of this region and/or mutations which vary from the DP178 sequence amino acid sequence. Further, certain of the
20 peptides have had amino- and/or carboxy-terminal groups either added or removed, as indicated in the figures; and

2) FIG. 50. presents peptides which represent truncations of DP107 and/or the gp41 region
25 surrounding the DP107 amino acid sequence of HIV-1 BRU isolate. Certain of the peptides are unblocked or biotinylated, as indicated in the figure.

Blocked peptides contained an acyl N-terminus and
30 an amido C-terminus.

28.2 RESULTS

Anti-HIV antiviral data was obtained with the group 1 DP178-derived peptides listed in FIG. 49A-C. The full-length, non-mutant DP178 peptide (referred to in FIG. 49A-C as T20) results shown are for 4ng/ml.

5 In FIG. 49A, a number of the DP178 truncations exhibited a high level of antiviral activity, as evidenced by their low IC_{50} values. These include, for example, test peptides T-50, T-624, T-636 to T-641, T-645 to T-650, T-652 to T-654 and T-656. T-50
10 represents a test peptide which contains a point mutation, as indicated by the residue's shaded background. The HIV-1-derived test peptides exhibited a distinct strain-specific antiviral activity, in that none of the peptides tested on the HIV-2 NIHZ isolate
15 demonstrated appreciable anti-HIV-2 antiviral activity.

Among the peptides listed in FIG. 49B, are test peptides representing the amino (T-4) and carboxy (T-3) terminal halves of DP178 were tested. The amino terminal peptide was not active ($IC_{50} > 400 \mu\text{g/ml}$) whereas
20 the carboxy terminal peptide showed potent antiviral activity ($IC_{50} = 3 \mu\text{g/ml}$). A number of additional test peptides also exhibited a high level of antiviral activity. These included, for example, T-61/T-102, T-217 to T-221, T-235, T-381, T-677, T-377, T-590, T-
25 378, T-591, T-271 to T-272, T-611, T-222 to T-223 and T-60/T-224. Certain of the antiviral peptides contain point mutations and/or amino acid residue additions which vary from the DP178 amino acid sequence.

In FIG. 49C, point mutations and/or amino and/or
30 carboxy-terminal modifications are introduced into the DP178 amino acid sequence itself. As shown in the

figure, the majority of the test peptides listed exhibit potent antiviral activity.

Truncations of the DP107 peptide (referred to in IG. 50 as T21) were also produced and tested, as shown in FIG. 50. FIG. 50 also presents data concerning
5 blocked and unblocked peptides which contain additional amino acid residues from the gp41 region in which the DP107 sequence resides. Most of these peptides showed antiviral activity, as evidenced by their low IC_{50} values.

10 Thus, the results presented in this Section demonstrate that not only do the full length DP107 and DP178 peptides exhibit potent antiviral activity, but truncations and/or mutant versions of these peptides can also possess substantial antiviral character.

15 29: EXAMPLE: POTENTIAL EPSTEIN-BARR DP178/DP107
ANALOGS: ANTIVIRAL CHARACTERIZATION

In the Example presented herein, peptides derived from the Epstein-Barr (EBV) DP-178/DP107 analog region of the Zebra protein identified, above, in the Example
20 presented in Section 20 are described and tested for anti-EBV activity. It is demonstrated that among these peptides are ones which exhibit potential anti-viral activity.

25 29.1 MATERIALS AND METHODS

Electrophoretic Mobility Shift Assays (EMSA):

Briefly, an EBV Zebra protein was synthesized utilizing SP6 RNA polymerase in vitro transcription and wheat germ in vitro translation systems (Promega Corporation recommendations; Butler, E.T. and
30 Chamberlain, M.J., 1984, J. Biol. Chem. 257:5772; Pelham, H.R.B. and Jackson, R.J., 1976, Eur. J.

Biochem. 67:247). The in vitro translated Zebra protein was then preincubated with increasing amounts of peptide up to 250 ng/ml prior to the addition of 10,000 to 20,000 c.p.m. of a ³²P-labeled Zebra response element DNA fragment. After a 20 minute incubation in
5 the presence of the response element, the reaction was analyzed on a 4% non-denaturing polyacrylamide gel, followed by autoradiography, utilizing standard gel-shift procedures. The ability of a test peptide to prevent Zebra homodimer DNA binding was assayed by the
10 peptide's ability to abolish the response element gel migration retardation characteristic of a protein-bound nucleic acid molecule.

Peptides: The peptides characterized in this study represent peptide walks through the region
15 containing, and flanked on both sides by, the DP178/DP107 analog region identified in the Example presented in Section 20, above, and shown as shown in FIG. 33. Specifically, the peptide walks covered the region from amino acid residue 173 to amino acid
20 residue 246 of the EBV Zebra protein.

Each of the tested peptides were analyzed at a range of concentrations, with 150ng/ml being the lowest concentration at which any of the peptides exerted an inhibitory effect.

25 29.2 RESULTS

The EBV Zebra protein transcription factor contains a DP178/DP107 analog region, as demonstrated in the Example presented, above, in Section 20. This protein appears to be the primary factor responsible
30 for the reactivation capability of the virus. A method by which the DNA-binding function of the Zebra virus may be abolished may, therefore, represent an

effective antiviral technique. In order to identify potential anti-EBV DP178/DP107 peptides, therefore, peptides derived from the region identified in Section 20, above, were tested for their ability to inhibit Zebra protein DNA binding.

5 The test peptides' ability to inhibit Zebra protein DNA binding was assayed via the EMSA assays described, above, in Section 28.1. The data summarized in FIG. 51A-B presents the results of EMSA assays of the listed EBV test peptides. These
10 peptides represent one amino acid "walks" through the region containing, and flanked on both sides by, the DP178/DP107 analog region identified in the Example presented in Section 20, above, and shown as shown in FIG. 33. As shown in FIG. 51A-B, the region from
15 which these peptides are derived lies from EBV Zebra protein amino acid residue 173 to 246. A number of the test peptides which were assayed exhibited an ability to inhibit Zebra protein homodimer DNA binding, including 439, 441, 444 and 445.

20 Those peptides which exhibit an ability to inhibit Zebra protein DNA binding represent potential anti-EBV antiviral compounds whose ability to inhibit EBV infection can be further characterized.

25 30. EXAMPLE: IDENTIFICATION OF RSV DP107/DP178
 ANALOGS WITH REDUCED BINDING
 AFFINITY

 In the example presented herein, peptides derived from the RSV DP178 analog T112 are described and tested for binding affinity to the DP107-like domain of the RSV F1-protein. Particular peptides are
30 identified that have a reduced binding affinity for their DP107-like target, and key amino acid residues

are identified the confer high binding affinity to the native peptide (*i.e.*, to T112). Such peptides are useful, *e.g.*, in screening assays such as those described above in Section 5.6.1 to identify compounds which inhibit or disrupt the interaction between DP107 and DP178, and in providing guidance for generation of additional peptides exhibiting reduced affinity binding.

30.1 MATERIALS AND METHODS

A maltose binding fusion protein of the RSV F1-protein (MF5.1) was constructed using methods similar to those described in Section 8.1.2, *supra*, for construction of the M41 fusion protein. Specifically, the DNA sequence corresponding amino acid residues 142-302 of the RSV F1 protein was amplified by PCR and cloned into the Xmn I site of the expression vector pMal-p2 (New England Biolab) to give MF5.1. These amino acid residues correspond to the extracellular domain of the RSV F1 protein including its DP107 region but excluding the DP178 region.

The peptides characterized in the study presented herein were: T122, T800, T801, T802, T803, T804, T805, T806, T807, T808, T809, T810, T811, T1669, T1670, T1671, T1672, T1673, T1680, T1681, T1682, T1683 and T1684, as shown in FIG. 53. T112 represents the DP178-like region of the RSV F1 protein. The other peptides characterized are modified DP178 proteins derived from T112.

Cell fusion assays were performed with each of the peptides as described in Section 17 above. The binding affinity of each peptide was also measured in a competitive binding assay described in Section 5.6.1

above, wherein the concentration of each peptide necessary to bind to the M5.1 fusion protein (i.e., the B_{50} value), and thereby disrupt binding of biotin labeled T112 (T888) to the fusion protein, was measured.

5

30.2 RESULTS

T112 is a 35 amino acid residue peptide that corresponds to amino acid residues 482-516 of the RSV F1 protein and has the following amino acid sequence:

10

VFPSDEFDASISQVNEKINQSLAFIRKSDELLHNV

The peptide represents the DP178-like region of the RSV F1 protein and has substantial antiviral activity against RSV as discussed in Section 17.2 above and shown in FIG. 28A.

15

T112 analogs were generated according to at least three different strategies to generate peptides based on T112 that would still bind to the DP107-like domain of the RSV F1 protein but with a lower binding affinity. First, a truncated peptide was generated, reducing the length of the peptide from 35 to 28 amino acid residues. Specifically, the truncated peptide, which is referred to herein as T67, had the amino acid sequence:

20

25

DEFDASISQVNEKINQSLAFIRKSDELL

corresponding to amino acid residues 486-213 of the F1 fusion protein. The binding affinity of the peptide to the DP107-like domain of F1 protein was determined according to the methods described in Section 5.6.1

30

above. The truncated peptide had a binding affinity (5 nM) that was five times lower than that of the full length T112 peptide (2 nM).

As part of a second strategy, the peptides identified as T800 through T811 in FIG. 53 were synthesized to identify particular amino acids in T112 that contribute to a larger part of that peptide's binding affinity. As a whole, these alanine substitutions represent an "alanine-scanning" type walk across the sequence of T112.

Each of the peptides synthesized had a change of three consecutive amino acid residues in the T112 sequence to three alanine residues. Each peptide was tested for its ability to inhibit the binding of the native peptide (i.e., of T112) in a competitive binding assay as described in Section 5.6.1 above. The results are also shown in FIG. 53. In particular, the peptides T802, T804, T807 and T810 had significantly reduced affinity for the DP107-like target, suggesting that the regions containing amino acid residues 488-490, 494-496, 503-505 and 512-514 of the RSV F1 protein (amino acid residues 7-9, 13-15, 22-24 and 31-33, respectively, of T112), contribute significantly to the high binding affinity of T112 for its DP107-like target in the RSV F1 protein.

The peptides T1669-T1673 and T1680 through T1684 were then synthesized, each of which contains a single alanine substitution at one of the above-listed amino acid residue positions of T112. The binding affinity of these peptides for their DP107-like target can also be determined by means of the same routine screening assays, thereby identifying individual amino acid residues which affect binding affinity of T112.

In addition, an additional novel peptide, referred to as T786, was generated by modifying various amino acid residues in the T112 sequence which were identified, using standard principles of protein and design, as affecting properties such as binding
5 affinity, solubility and biological stability. Specifically the following amino acid residue substitutions were made: F₂ - Y, S₂₁ - A, F₂₄ - Y and S₂₈ - A, wherein the subscript numerals indicate the amino acid residue position in T112. The resultant
10 peptide, which is referred to herein as T786, thus had the amino acid sequence:

VYPSDEFDASISQVNEKINQALAYIRKADELLHNV

15 The binding affinity of this novel peptide for the DP107 target was found to be 19 nM, i.e., approximately ten-fold less than the binding affinity of T112.

The data demonstrates that peptides having a reduced binding affinity for a DP107 target (i.e., for
20 an HR1 domain) may be readily found by modifying a DP178 peptide such as T112, e.g., by means of the routine techniques and assays described herein. Further, the techniques and assays identify key amino acid residues which may be used to construct and
25 identify other reduced affinity peptides.

31. EXAMPLE: IDENTIFICATION OF HIV DP107/DP178
ANALOGS WITH REDUCED BINDING
AFFINITY

In the example presented herein, peptides derived
30 from DP178, which is also referred to as T20, are described and tested for binding affinity to the DP107

domain of the HIV gp41. Particular peptides are identified that have a reduced binding affinity for their DP107 target, and key amino acid residues are identified the confer high binding affinity to the native peptide (*i.e.*, to T20). Such peptides are
5 useful, *e.g.*, in screening assays such as those described above in Section 5.6.1 to identify compounds which inhibit or disrupt the interaction between DP107 and DP178.

Specifically, the peptides identified as T813 and
10 T868 through T878 in FIG. 53 were synthesized to identify particular amino acids in T20 (DP178) that contribute to a greater part of that peptide's binding affinity. Each of the peptides synthesized had a change of three consecutive amino acid residues in the
15 T20 sequence to three alanine residues. The antiviral activity of each peptide was assayed in cell fusion assays as described in Section 6.1.3, above. The binding affinities of the peptides were also measured in a competitive binding assay described in Section 5.6.1 above, wherein each peptides ability to disrupt
20 the binding of either biotin (T83) or fluorescein (T1342) labeled DP178 (T20) to the M41Δ178 fusion protein described in Section 8, above, was measured. The binding affinity of each peptide to the peptide referred to as T764
25 (GSTMGARSMTLTVQARQLLSGIVQQNNLLRAIEAQQH) also measured using circular dichroism to monitor the amount of secondary structure (*i.e.*, helicity) adopted by the peptides. T764 is a peptide which represents the DP107 target domain of DP178 (T20).

30 The results are provided in FIG. 54. In particular, the peptides T813, T878, T874-T876 and

T871 have significantly reduced affinity for the DP107 region, suggesting the regions corresponding to the substituted amino acid residues in those peptides contribute significantly to the high binding affinity of T20. The peptides T1627-T1632, T1650-T1653 and
5 T1656-T1665 were then synthesized. Each of these peptides contains a single alanine substitution at one of the amino acid residues in one of the regions identified as contributing significantly to the high binding affinity of T20. Identical assays which
10 measured the binding affinity of these peptides identified four essential residues (I₆₄₆, Q₆₅₂, Q₆₅₃ and N₆₅₆, with the subscript numerals indicating the residue position in the HIV-1_{LAI} gp41 amino acid sequence) in which alanine-substitution completely
15 prevented binding to the DP107 domain, as well as five residues (L₆₄₁, I₆₄₂, I₆₄₅, E₆₅₇ and L₆₆₃, with the subscript numerals indicating the residue) in which alanine-substitution position in the HIV-1_{LAI} gp41 amino acid sequence) that reduced the binding affinity but did not actually block binding to the DP107
20 domain.

The data demonstrates that peptides having a reduced binding affinity for a DP107 target (*i.e.*, for an HR1 domain) may be readily found by modifying a DP178 peptide such as T20, *e.g.*, by means of the
25 routine techniques and assays described herein. Further, the techniques and assays identify key amino acid residues which may be used to construct and identify other reduced affinity peptides.

30

The present invention is not to be limited in scope by the specific embodiments described which are intended as single illustrations of individual aspects of the invention, and functionally equivalent methods and components are within the scope of the invention.

5 Indeed, various modifications of the invention, in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and accompanying drawings. Such modifications are intended to fall within the scope of
10 the appended claims.

15

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WHAT IS CLAIMED IS:

1. A method for identifying a compound that inhibits the formation of or disrupts a DP107/DP178
5 complex comprising:
 (a) preparing, both in the presence and in the absence of a test compound, a reaction mixture containing a DP107 peptide and a DP178 peptide under conditions and for a
10 time sufficient to allow formation of a DP107/DP178 complex; and
 (b) detecting the formation of a DP107/DP178 complex both in the presence and in the absence of the test compound,
15 wherein the formation of a DP107/DP178 complex in the absence, but not in the presence of the test compound indicates that the compound inhibits the formation of or disrupts a DP107/DP178 complex.
2. The method of Claim 1, wherein the DP107
20 peptide or the DP178 peptide is a modified DP107 or DP178 peptide.
3. The method of Claim 2 wherein the modified DP107 or DP178 peptide has a reduced binding affinity.

25

30

HIV1LAI (DP-178; SEQ ID:1)	YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNMF
HIV1SF2 (DP-185; SEQ ID:3)	YTNTIYNLLEESQNQQEKNEQELLELDKWASLWNMF
HIV1RF (SEQ ID:4)	YTGIIYNLLEESQNQQEKNEQELLELDKWANLWNMF
HIV1MN (SEQ ID:5)	YTSLIYSLLEKSQTQQEKNEQELLELDKWASLWNMF
HIV2ROD (SEQ ID:6)	LEANISKSLEQAQIQQEKNNMYELQKLSWDIFGNMF
HIV2NIHZ (SEQ ID:7)	LEANISQSLEQAQIQQEKNNMYELQKLSWDVFTNWL
DP180 (SEQ ID:2)	SSSFITLLEQWNNWKLQAEQWLEQINEKHYLEDIS
DP118 (SEQ ID:10)	QQLLDVVKRQQEMLRLTWGTKNLQARVTAIEKYLKDD
DP125 (SEQ ID:8)	CCGNNLLRAIEAQQHLLQLTWGIKQLQARILAVERYLKDD
DP116 (SEQ ID:9)	LQARILAVERYLKDDQQ

FIG.1

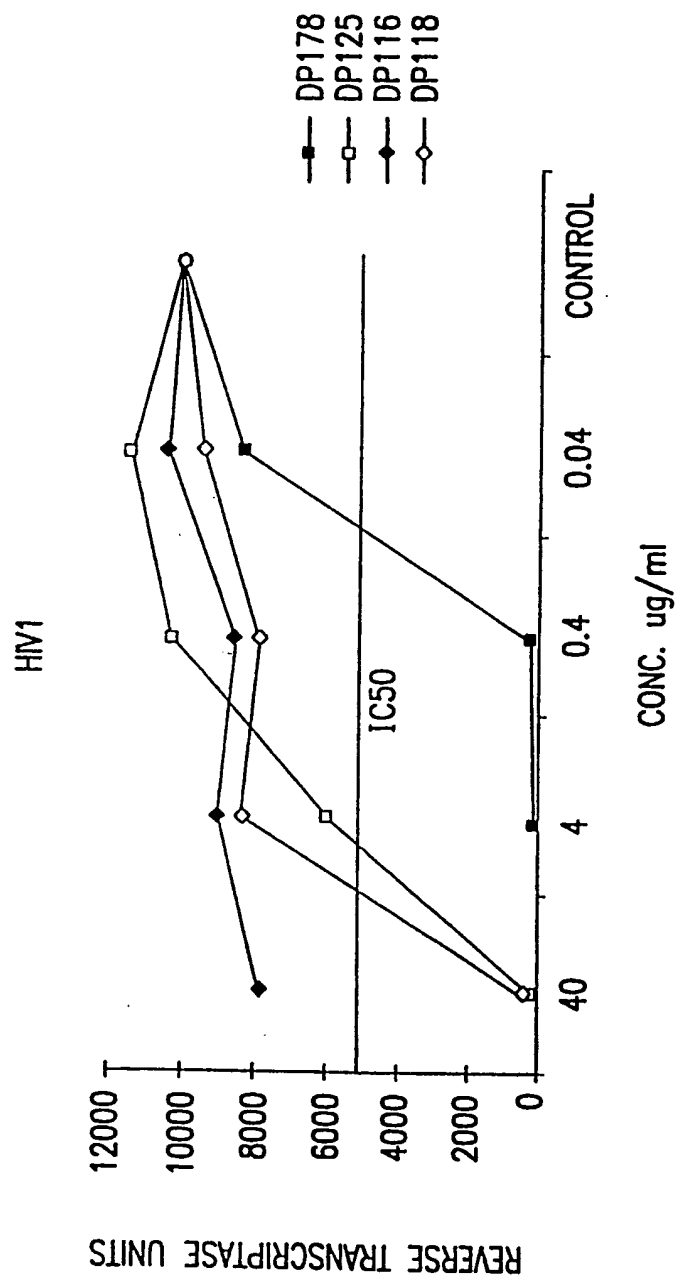


FIG.2

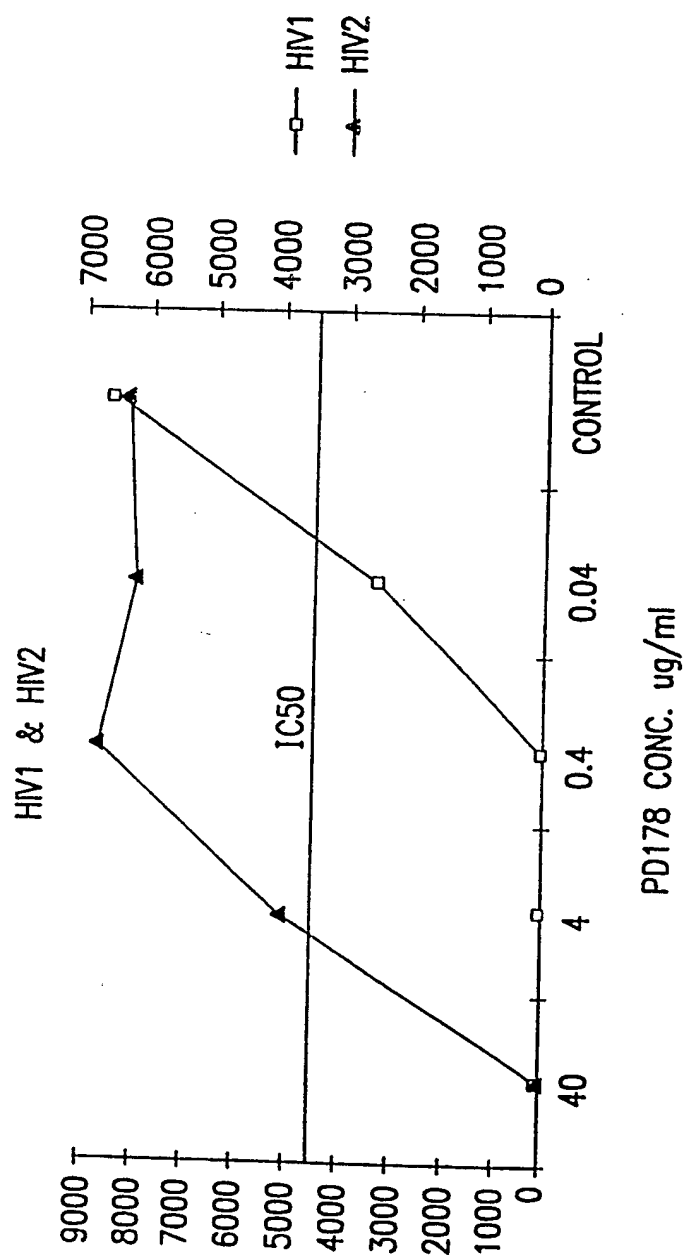


FIG.3

Number of Syncytia/well: concentration in $\mu\text{g/ml}$ (micrograms/ml)									
DP178	10	5	1	0.2	0.1	0.05	0.025	0.0125	Control
<i>Syncytia</i>									
HIV1LAT	0	0	0	0	0	0	0	0	67
HIV1MN	0	0	0	0	0	ND	ND	ND	34
HIV1RF	0	0	0	0	0	ND	ND	ND	65
HIV1SF2	0	0	0	0	0	ND	ND	ND	58
DP125	10	5	1	0.2	0.1	0.05	0.025	0.0125	Control
<i>Syncytia</i>									
HIV1LAT	0	0	54	69	80	75	79	82	67
HIV1MN	0	0	30	36	ND	ND	ND	ND	34
HIV1RF	0	0	67	63	ND	ND	ND	ND	65
HIV1SF2	0	0	9	66	ND	ND	ND	ND	58
DP116	10	5	1	0.2	0.1	0.05	0.025	0.0125	Control
<i>Syncytia</i>									
HIV1LAT	75	ND	ND	ND	ND	ND	ND	ND	67
HIV1MN	35	ND	ND	ND	ND	ND	ND	ND	34
HIV1RF	81	ND	ND	ND	ND	ND	ND	ND	65
HIV1SF2	81	ND	ND	ND	ND	ND	ND	ND	58

FIG.4A

DP180	40	20	10	5	2.5	1.25	0.625	0.3125	Control
<i>Syncytia</i>									
HIV1LAT	50	>45	>45	>45	>45	>45	>45	>45	58
DP185	40	20	10	5	2.5	1.25	0.625	0.3125	Control
<i>Syncytia</i>									
HIV1LAT	0	0	0	0	0	0	0	ND	60

FIG.4B

<u>HIV1</u>								
Number of Syncytia/well: concentration in ng/ml (nanograms/ml)								
DP178	20	10	5	2.5	1.25	0.625	0.3125	Control
<u>Syncytia</u>								
HIV1	0	0	0	0	0	14	20	48
DP116	20	10	5	2.5	1.25	0.625	0.3125	Control
<u>Syncytia</u>								
HIV1	ND	48	ND	ND	ND	ND	ND	ND
<u>HIV2</u>								
Number of Syncytia/well: concentration in μ g/ml (micrograms/ml)								
DP178	20	10	5	2.5	1.25	0.625	0.3125	Control
<u>Syncytia</u>								
HIV2	50	54	55	57	63	77	78	76
DP116	20	10	5	2.5	1.25	0.625	0.3125	Control
<u>Syncytia</u>								
HIV2	ND	58	ND	ND	ND	ND	ND	ND

FIG.5

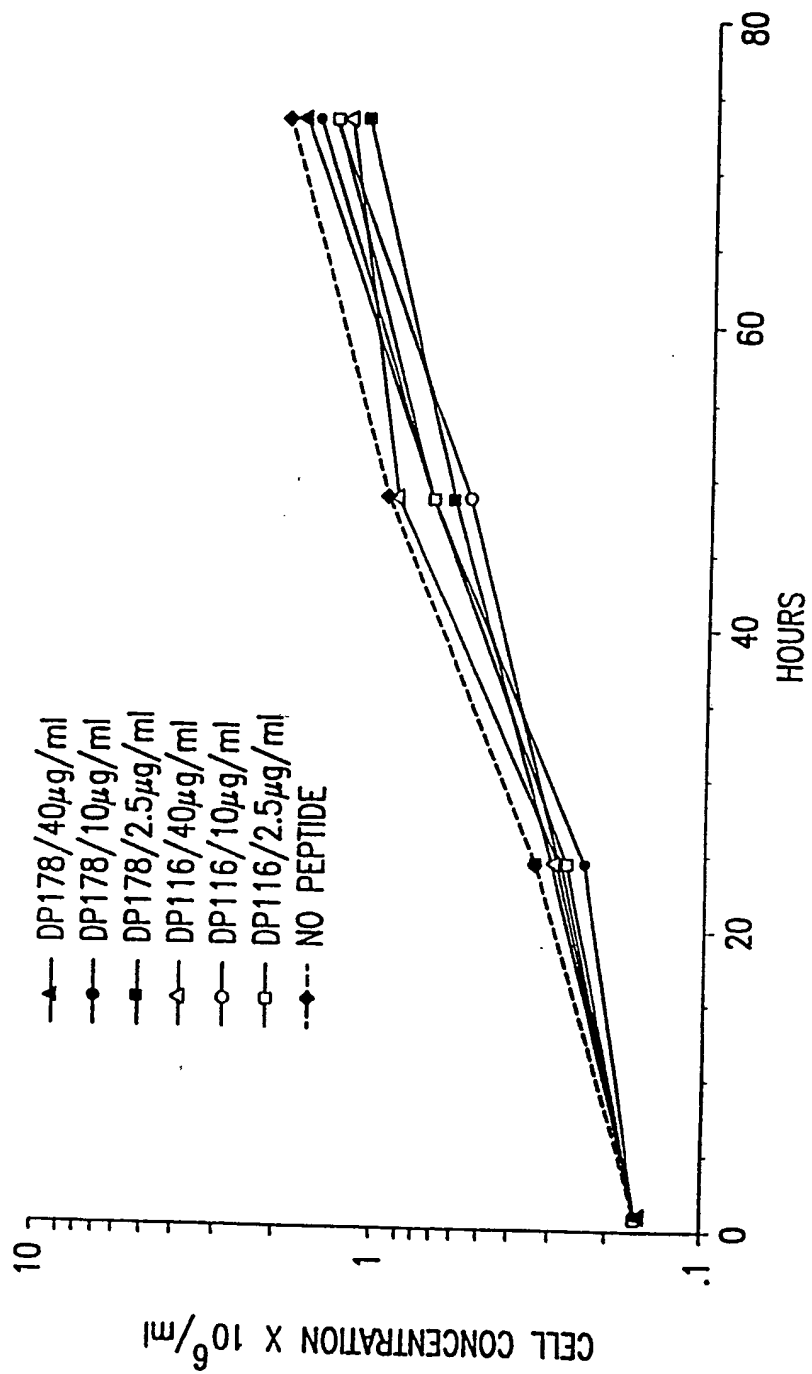


FIG.6

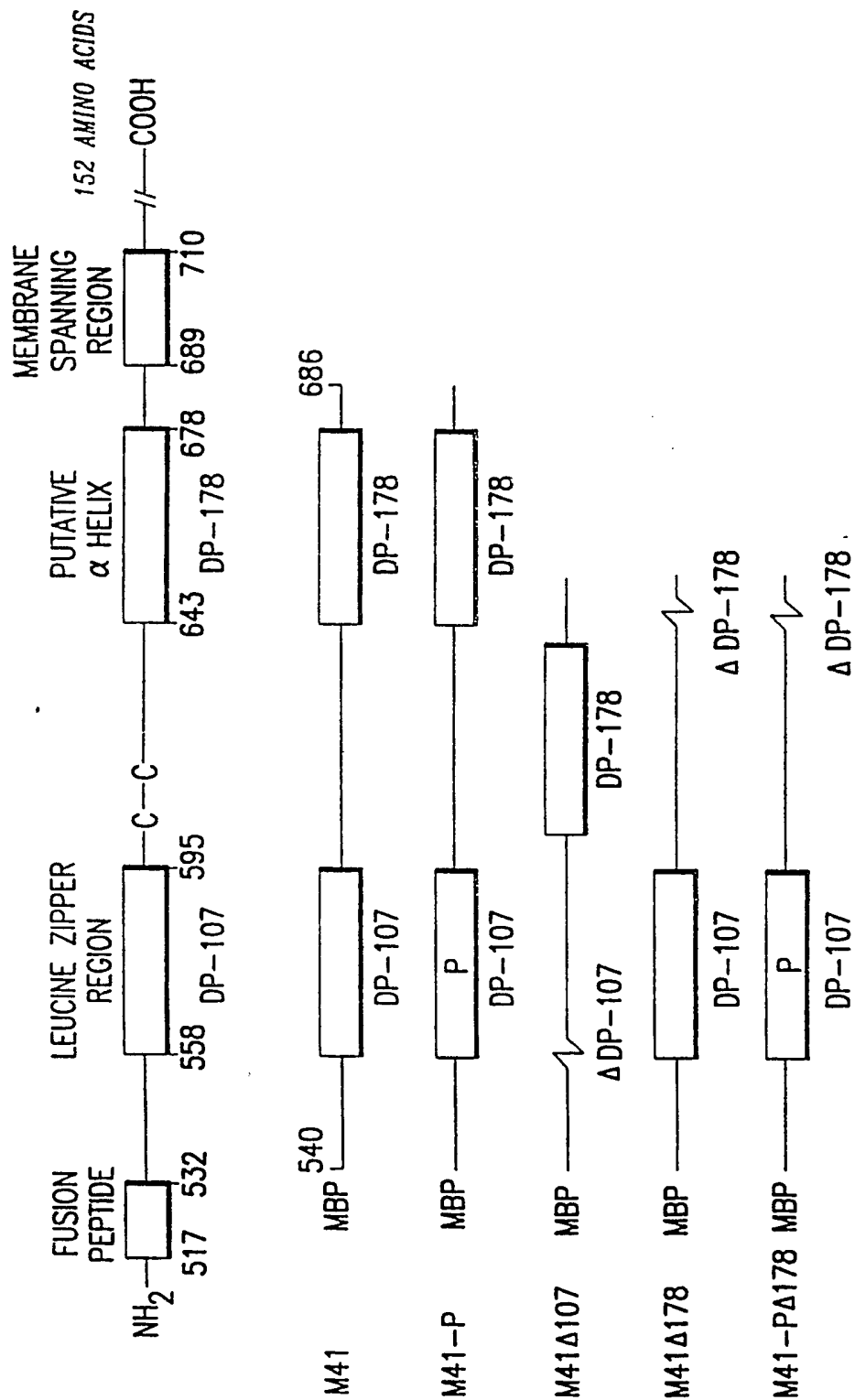


FIG.7

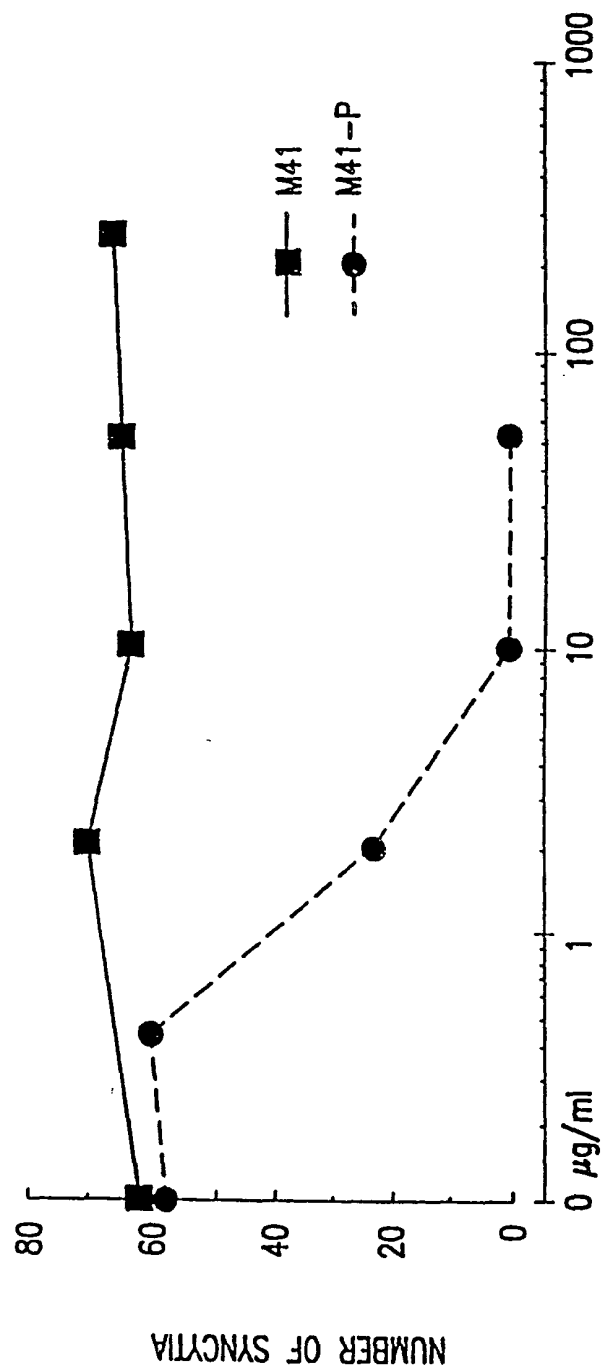


FIG.8

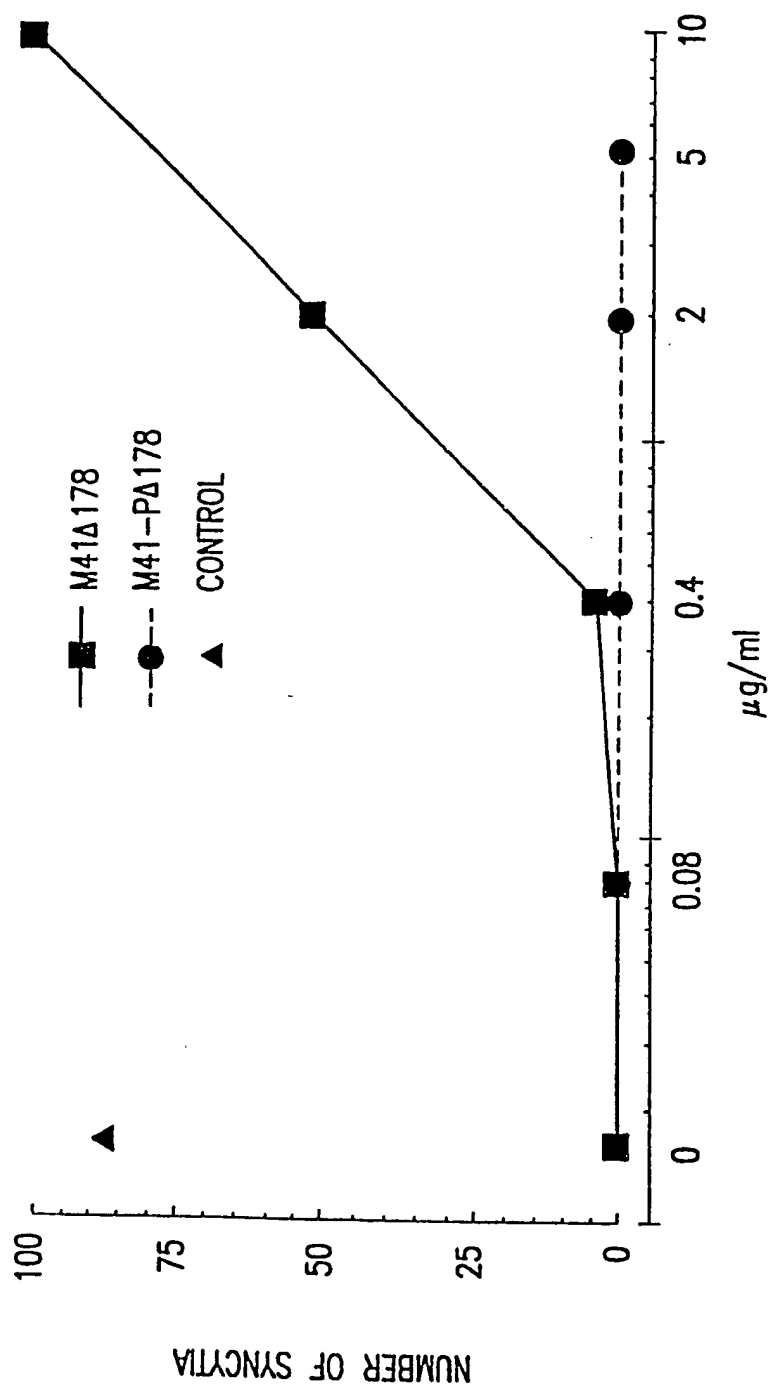


FIG.9

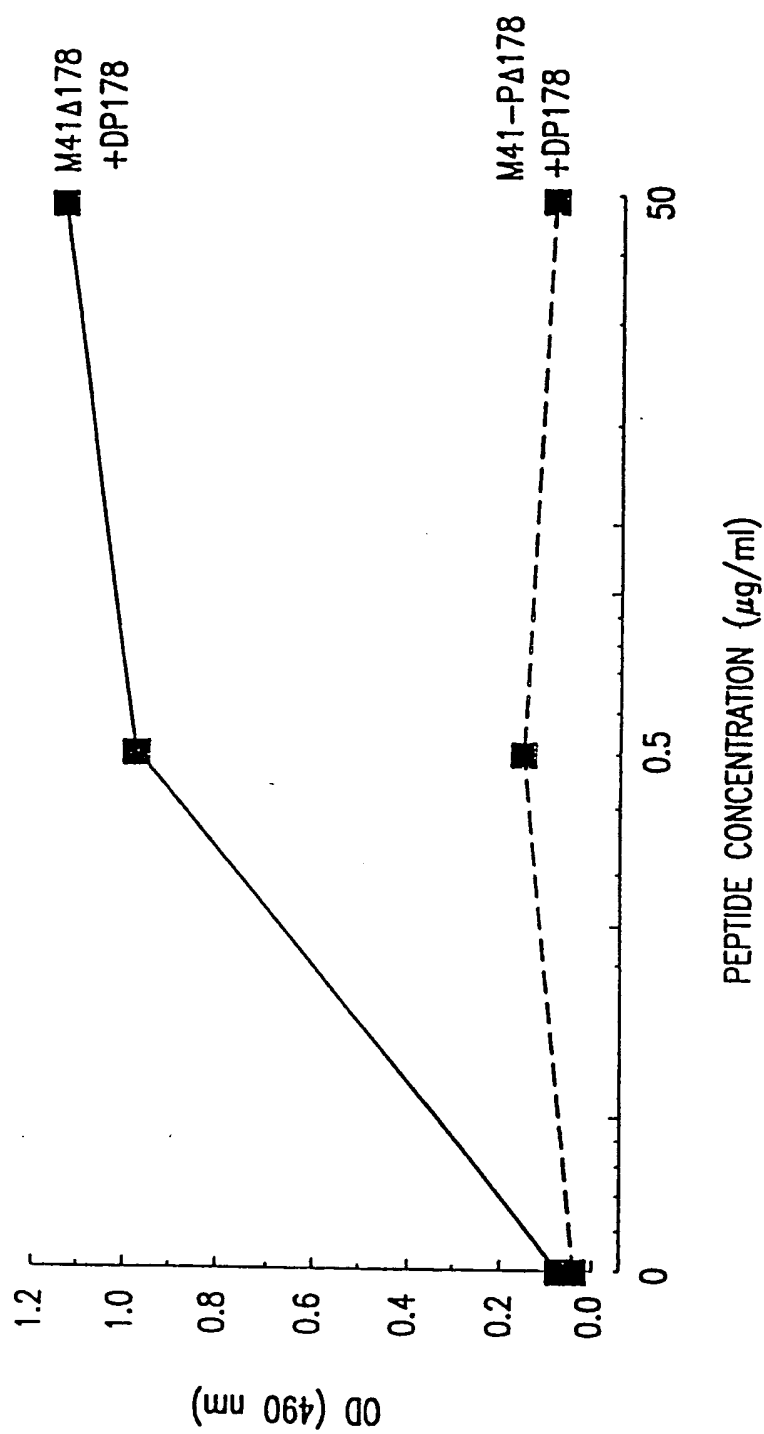


FIG.10

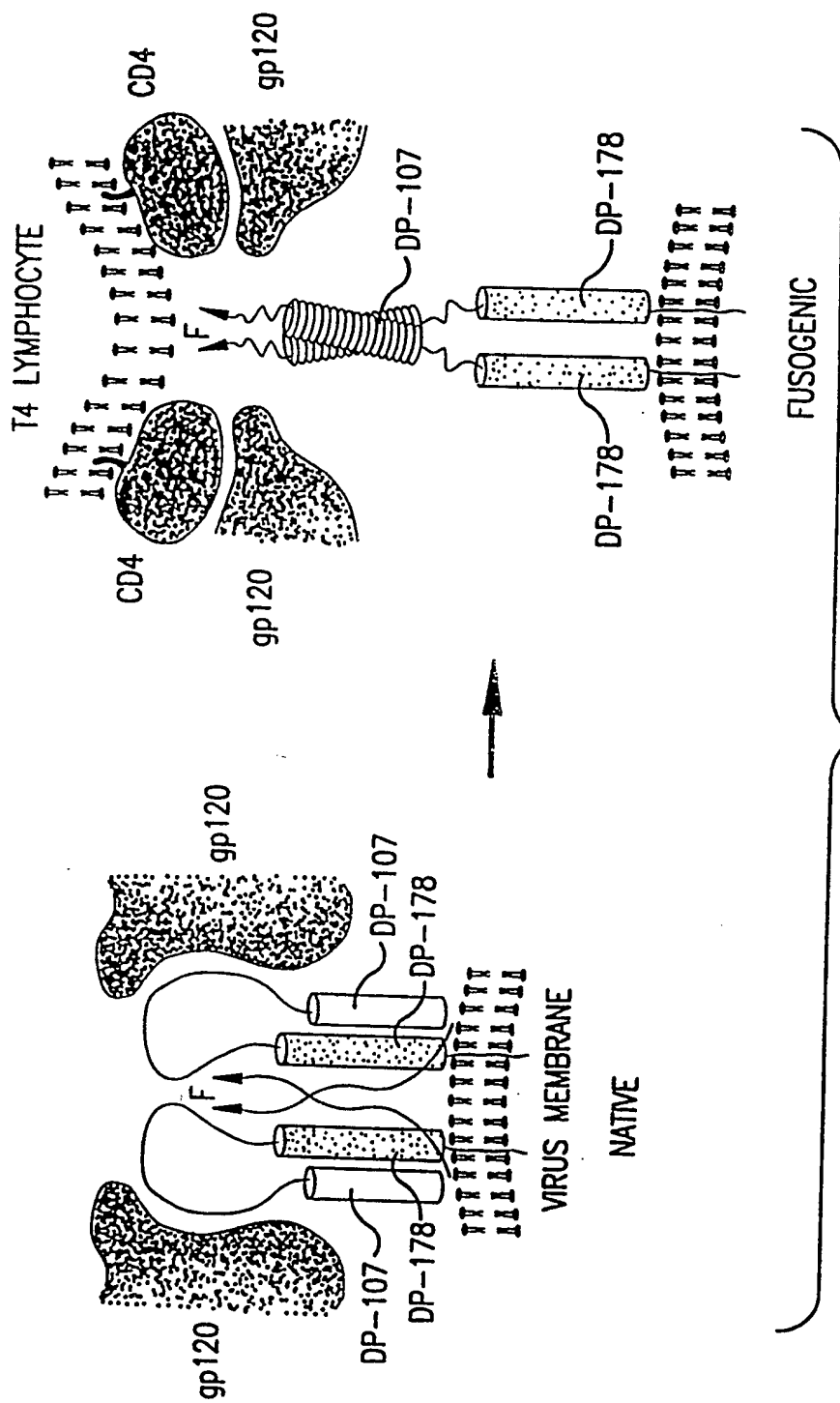
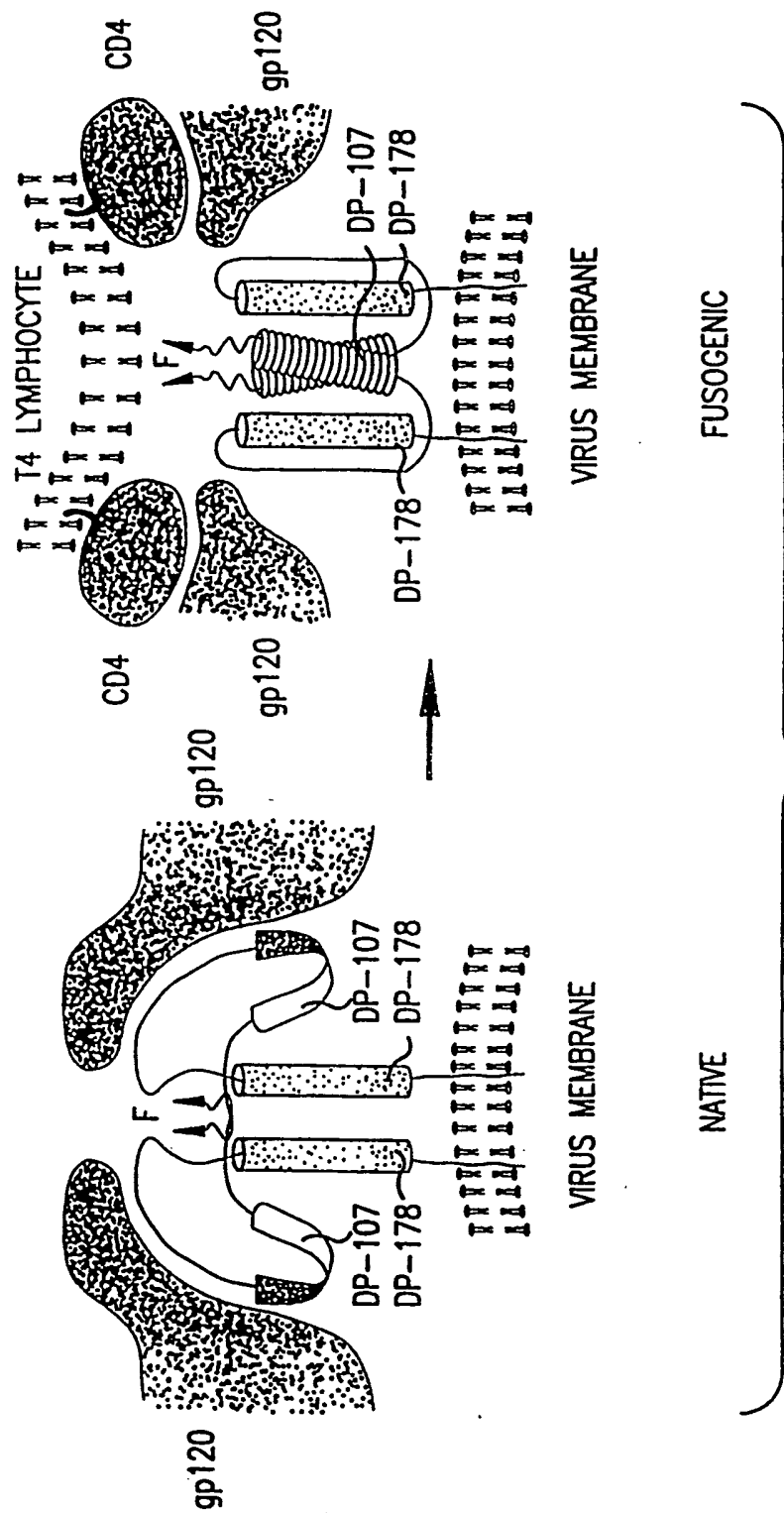


FIG.11A



Sequence	A	D	A	D	A	D	A	D	A	D	A	D	A	D	A	D	A	D	Motifs										
GCN4- (gcn4 yeast)	M	K	Q	L	E	D	K	V	E	E	L	S	K	N	H	L	E	N	E	V	A	R	L	K	K	L	[LMNV] {CFGIMPTW}		
C-FOS (fos_human)	T	D	T	L	Q	A	E	T	D	Q	L	E	D	E	K	S	A	L	Q	T	E	I	A	N	L	L	K	[IKLT] {CFGHMPRWY}	
C-JUN (lap1_human)	I	A	R	L	E	E	K	V	K	T	L	K	A	Q	N	S	E	L	A	S	T	A	N	M	L	R	E	[ALNV] {CDFGHILPWW}	
C-MYC (myo_human)	E	Q	K	L	I	S	E	E	D	L	L	E	K	R	R	E	Q	L	K	H	K	L	E	Q	L	R	N	S	[ELR] {ACFGMPWY}
FLU LOOP 36	I	E	K	T	N	E	K	F	H	Q	I	E	K	E	F	S	E	V	E	G	R	I	Q	D	L	E	K	Y	[FILT] {ACFLMPTW}

FIG. 12

Sequence	A	D	A	D	A	D	A	D	A	D	A	D	A	D	Motifs
DP-107 (env_hv1bru) L1=D	N	L	L	R	A	I	E	A	Q	H	L	L	Q	L	{ILOT} {CFIMPSTY}
DP-107 (env_hv1bru) L1=D	N	L	L	R	A	I	E	A	Q	H	L	L	Q	L	{ILOTV} {CDFIMPST}
DP-107 (env_hv1bru) L1=D	N	L	L	R	A	I	E	A	Q	H	L	L	Q	L	{ILOTV} {CDFIMPST}
DP-107 (env_hv1bru) L2=D	N	L	L	R	A	I	E	A	Q	H	L	L	Q	L	{EKLNV} {CDFKMPSTY}
DP-107 (env_hv1bru) L2=D	N	L	L	R	A	I	E	A	Q	H	L	L	Q	L	{EKLNV} {CFKAPS}
DP-107 (env_hv1bru) L2=D	N	L	L	R	A	I	E	A	Q	H	L	L	Q	L	{EKLNV} {CFKAPS}
DP-178 (env_hv1bru) Y1=A	Y	T	S	L	I	H	S	L	I	E	S	Q	N	Q	{EKLNV} {ACFGMPRVY}
DP-178 (env_hv1bru) Y1=A	Y	T	S	L	I	H	S	L	I	E	S	Q	N	Q	{EKLNV} {CFGMPRVY}
DP-178 (env_hv1bru) Y1=A	Y	T	S	L	I	H	S	L	I	E	S	Q	N	Q	{EKLNV} {CFGMPRVY}
DP-178 (env_hv1bru) Y1=D	Y	T	S	L	I	H	S	L	I	E	S	Q	N	Q	{EKLNV} {ACFGMPRVY}
DP-178 (env_hv1bru) Y1=D	Y	T	S	L	I	H	S	L	I	E	S	Q	N	Q	{EKLNV} {CFGMPRVY}
DP-178 (env_hv1bru) Y1=D	Y	T	S	L	I	H	S	L	I	E	S	Q	N	Q	{EKLNV} {CFGMPRVY}

FIG.13

Sequence	Positions												Parent Motif	Hybrid Motif		
	A	D	A	D	A	D	A	D	A	D	A	D				
GCN4 (gcn4 yeast)	M	K	Q	L	E	D	K	V	E	L	S	K	N	Y	[LMNV]	{CFGIMPTW}
DP-178 (env_hv1bru)Y1=A	Y	T	S	L	I	H	S	L	I	E	E	S	Q	N	[EKLOY]	{ACFGMPRVWY}
DP-178 (env_hv1bru)Y1=A	Y	T	S	L	I	H	S	L	I	E	E	S	Q	N	[EKLOWY]	{CFGMPRVY}
DP-178 (env_hv1bru)Y1=A	Y	T	S	L	I	H	S	L	I	E	E	S	Q	N	[EFKLQWY]	{CFGMPRVY}
DP-178 (env_hv1bru)Y1=D	Y	T	S	L	I	H	S	L	I	E	E	S	Q	N	[EILNOSY]	{ACFGMPRVWY}
DP-178 (env_hv1bru)Y1=D	Y	T	S	L	I	H	S	L	I	E	E	S	Q	N	[EILNOSWY]	{CFGMPRVY}
DP-178 (env_hv1bru)Y1=D	Y	T	S	L	I	H	S	L	I	E	E	S	Q	N	[EFILNOSWY]	{CFGMPRVY}

FIG.15

Sequence	Positions																Parent Motif	Hybrid Motif																			
	A	D	A	D	A	D	A	D	A	D	A	D	A	D	A	D																					
DP-107 (env_hv1bru) L1=D	N	N	L	R	A	I	E	A	Q	H	L	L	Q	L	T	V	W	G	I	K	Q	L	D	A	R	I	L	A	V	E	R	Y	L	K	D	Q	[ILQTV] {CDFIMPST}
DP-107 (env_hv1bru) L2=D	N	N	L	R	A	I	E	A	Q	H	L	L	Q	L	T	V	W	G	I	K	Q	L	D	A	R	I	L	A	V	E	R	Y	L	K	Q	[EKLNOV] {CFKAPS}	
DP-178 (env_hv1bru) Y1=A	Y	T	S	L	I	H	S	L	I	E	S	Q	N	Q	E	K	N	E	Q	E	L	L	E	L	D	K	W	A	S	L	W	N	W	F	[EKLQNY] {CEGAPRY}		
DP-178 (env_hv1bru) Y1=D					Y	T	S	L	I	H	S	L	I	E	S	Q	N	Q	E	K	N	E	Q	E	L	L	D	K	W	A	S	L	W	N	W	F	[EFLNOSNY] {CEGAPRY}
FLU LOOP 36	I	E	K	T	N	E	K	F	H	Q	I	E	K	E	F	S	E	V	E	G	R	I	D	L	E	K	Y									[FILTV] {ACFLMPTWH}	

FIG.16

Sequence	A	D	A	D	A	D	A	D	A	D	Parent Motif	Hybrid Motif
GCN4 (gcN4 yeast)	MKQL	EDKV	EEEL	LSKN	YHLE	NEV	ARL	KKL			[LMNV] {CFGIMP}TW	
DP-107 (env_hv1bru) L1=D	NNLL	RAIE	AQHL	LQLT	VWGI	KQLQ	ARIL	AVERY	LK	DQ	[ILOTV] {COFIMP}ST	
DP-178 (env_hv1bru) Y1=A	YTSL	IMSL	IEES	QNQ	QEKNE	QEL	LELD	KWA	SL	WNWF	[EFKLQWY] {CFGMPRY}	[EFIKLQWYVY] {CFMP}
GCN4 (gcN4 yeast)	MKQL	EDKV	EEEL	LSKN	YHLE	NEV	ARL	KKL			[LMNV] {CFGIMP}TW	
DP-107 (env_hv1bru) L1=D	NNLL	RAIE	AQHL	LQLT	VWGI	KQLQ	ARIL	AVERY	LK	DQ	[ILOTV] {COFIMP}ST	
DP-178 (env_hv1bru) Y1=D		YTSL	IHS	LSLIEES	QNQ	QEKNE	QEL	LELD	KWA	SLWNWF	[EFILQWSTWYVY] {CFGMPRY}	[EFILQWSTWYVY] {CFMP}
GCN4 (gcN4 yeast)	MKQL	EDKV	EEEL	LSKN	YHLE	NEV	ARL	KKL			[LMNV] {CFGIMP}TW	
DP-107 (env_hv1bru) L2=D	NNLL	RAIE	AQHL	LQLT	VWGI	KQLQ	ARIL	AVERY	LK	DQ	[EKLNV] {CFKAPS}	
DP-178 (env_hv1bru) Y1=A	YTSL	IHS	LSLIEES	QNQ	QEKNE	QEL	LELD	KWA	SL	WNWF	[EFKLQWY] {CFGMPRY}	[EFLQWYVY] {CFMP}
GCN4 (gcN4 yeast)	MKQL	EDKV	EEEL	LSKN	YHLE	NEV	ARL	KKL			[LMNV] {CFGIMP}TW	
DP-107 (env_hv1bru) L2=D	NNLL	RAIE	AQHL	LQLT	VWGI	KQLQ	ARIL	AVERY	LK	DQ	[EKLNV] {CFKAPS}	
DP-178 (env_hv1bru) Y1=D		YTSL	IHS	LSLIEES	QNQ	QEKNE	QEL	LELD	KWA	SLWNWF	[EFILQWSTWYVY] {CFGMPRY}	[EFLQWYVY] {CFMP}

FIG. 17

Sequence	Positions												Parent Motif	Hybrid Motif	
	A	D	A	D	A	D	A	D	A	D	A	D			
GCN4 (gcn4 yeast)	M	K	Q	L	E	D	K	V	E	E	L	S	K	N	[LMNV] {CEGIMPTH}
DP-107 (env_hv1bru) L1=D	N	N	L	L	R	A	I	E	A	Q	H	L	L	Q	[ILOTV] {CDFIMPST}
DP-107 (env_hv1bru) L2=D	N	N	L	L	R	A	I	E	A	Q	H	L	L	Q	[EKLNV] {CFKAPS}
DP-178 (env_hv1bru) Y1=A	Y	T	S	L	I	H	S	L	I	E	E	S	O	N	[EFKLQWY] {CEGMPRVY}
DP-178 (env_hv1bru) Y1=D	Y	T	S	L	I	H	S	L	I	E	E	S	O	N	[EFILNOSWY] {CEGMPRVY}
C-FOS (fos_human)	T	D	T	L	Q	A	E	T	D	Q	L	E	L	L	[IKLT] {CEGHMPRVWY}
C-JUN (jun1_human)	I	A	R	L	E	E	K	V	K	T	L	K	A	Q	[AILNV] {CDFGHILPVWY}
C-MYC (myc_human)	E	Q	K	L	I	S	E	E	D	L	L	E	K	R	[ELR] {ACFGMPVWY}
FLU LOOP 36	I	E	K	T	N	E	K	F	H	Q	I	E	K	E	[FILTV] {ACFLMPTVWY}

[AEF IKLMNQRSTVWY] {CFP}
= {CDGHP} {CFP}

FIG.18

$P-[LIV]-\{P\}(6)-[LIV]-\{P\}(6)-[LIV]$
 $P-\{P\}(1)-[LIV]-\{P\}(6)-[LIV]-\{P\}(6)-[LIV]$
 $P-\{P\}(2)-[LIV]-\{P\}(6)-[LIV]-\{P\}(6)-[LIV]$
 $P-\{P\}(3)-[LIV]-\{P\}(6)-[LIV]-\{P\}(6)-[LIV]$
 $P-\{P\}(4)-[LIV]-\{P\}(6)-[LIV]-\{P\}(6)-[LIV]$
 $P-\{P\}(5)-[LIV]-\{P\}(6)-[LIV]-\{P\}(6)-[LIV]$
 $P-\{P\}(6)-[LIV]-\{P\}(6)-[LIV]-\{P\}(6)-[LIV]$
 $P-\{P\}(7)-[LIV]-\{P\}(6)-[LIV]-\{P\}(6)-[LIV]$
 $P-\{P\}(8)-[LIV]-\{P\}(6)-[LIV]-\{P\}(6)-[LIV]$
 $P-\{P\}(9)-[LIV]-\{P\}(6)-[LIV]-\{P\}(6)-[LIV]$
 $P-\{P\}(10)-[LIV]-\{P\}(6)-[LIV]-\{P\}(6)-[LIV]$
 $P-X(1,12)-[LIV]-\{P\}(6)-[LIV]-\{P\}(6)-[LIV]$
 $P-X(13,23)-[LIV]-\{P\}(6)-[LIV]-\{P\}(6)-[LIV]$

FIG.19

Fusion Peptide
 ♡.....ELGELG ♡ ALLMOTIS ♡ A AGSTMGARSM TLTVQARQ ♡^{107x178x4}LLSGIVQQQ DP107-NNL
LRAIEAQOHLLOLTVVGIKQLOARILAYER YLKDO-DP107 QLLG ♡ ♡ IWGC
 ♡ ALLMOTIS ♡ ♡^{107x178x4}LVS Coiled-Coil*
 SGKLICT TAVP ♡ WNASWS NKSLEQIWNN MTWM *E ♡ WDREINN DP178-
YTSLIHSL IEESONQOEK NEOELLELDK* WASLIYNT-DP178 NI
 ♡ Transmembrane Region ♡
 TNWLWYIK ♡ ♡^{107x178x4}IMIVGGLVGLRIVEAVLSIV NRVROGYS ♡ PL
 ♡ P23LZIPC ♡
 SFQTHLP TPR GPDR ♡ PEGIEE EGGERDRDRS IRLVNGSLAL IWDDLRLS ♡ CL
 ♡ ALLMOTIS ♡ ♡^{107x178x4}EALKY WWNLLQYWSQ
 F ♡ SYHRLRDLL LIVTRIVELL GRRGW ♡
ELKNSAVSLL NAT ♡ ALAVAEG TDRVIEVVQG A ♡ CRAIRHIPR
 RIRQGLERIL L

FIG. 20

Fusion ♡ALLMOTI5♡
 Peptide ♡107x178x4♡
 ♡.....ELGEL LGVGSALAS GVA ♡YSKVLHL EGEVNKIKSA

 ♡P1&12LZIPC♡
LLSTNKAVVSLSNGVSVLTS KVLDLKQYID KQ ♡ ♡ LL ♡PIVNKQ

 ♡107x178x4♡
 SC ♡SISNIETVI ♡ EFOQKNNRLL EITREFSYNAG ♡ VITP'VSTMLTNSSELLSL

 ♡P1&12LZIPC♡
 ♡ALLMOTI5♡
 INDM ♡PI ♡TNDQ KKLMSNNVQI V ♡ RQSYSI ♡ MS IIKEEVLAYV

VQ ♡ LPLYGVID TPCWKLIITSP LCTTNTKEGS NICLTRTDRG WYCDNAGSVS

FFPQAETCKV QSNRVFCDTM NSLTLPSEIN LCNVDIFNPK

YDCKIMTSKT DVSSSVITSL GAIVSCYGKT KCTASNKNRG

IIKTFSNGCDYVSNKGMDTV SVGNTLYYVN KQEGKSLYVK G

 ♡P7, 12, & 23LZIPC♡
 ♡107x178x4♡ ♡ALLMOTI5♡
 EPIHNFYDPLVF ♡PSDE ♡EDASISQYNEKINQSLAF ♡I ♡ RKSDELL ♡

 ♡Transmembrane Region ♡
IINVNA ♡ GK STTN ♡IMITLIIVIVILLS LIAVGLLLY ♡ C ♡

KARSTPVTLS KDQLSGINNI AFSN

FIG. 21

Fusion
 Peptide ♡ ALLMOTIS ♡ ♡ 107x178x4 ♡
 ELGELG ♡ AAGTA MGAAA ♡ TALTVQSQHLLAGILOQQKNLLAAV

♡ 107x178x4 ♡
 EAQ ♡ QQM ♡ LKLTWGVKNLNARVTALEKYLEDOARLN ♡ AWG ♡ CA

♡ LVS Coiled-Coil ♡
 ♡ ALLMOTIS ♡ ♡ 107x178x4 ♡
 WKQVCHTIVP WQWNNRTPDW ♡ NNMT ♡ WLE ♡ WEROISYLEGNTT

♡ 107x178x4 ♡
TOLEEARAOEEKNLD ♡ AYOKLSS ♡ WSDFWSW ♡ FDF ♡ SKWLN ♡ ILK

♡ Transmembrane Region ♡
IGELDYLGIGLRLLYTV ♡ YS ♡ CIARVRQGYS PLSPQIHHTP WKGQPDNAEG

PGE GGD KRKN SSEPWQKESG TAEWKS NWCK RL TNWCSISS IWL YNS

♡ ALLMOTIS ♡
 ♡ CLTL LVHLRSAFQY IQYGLGELKA AAQEAVVALA RLAQNAGYQIWL ♡

ACRSAYRA IINSPRRVRQ GLEGILN

FIG. 22

Fusion *107x178x4*
 Peptide *LVS Coiled-Coil*
EAG *SNLNAQAIO
*VYL AGVALGVATA AQITAGIALHQ

SLRTSLEQSNKAIEEIREATOETVIA* VOGVQDY* VNNEL* VP

ALLMOTI5
107x178x4
P6 & 12LZIPC
 AMQHMSCELVGQRLGLRLLRYYTELLSIFGPSLRD *PISA *EISIQALIAL

GGEDIKLEKLGYSGSD* MIALESRGIKTKI* THVDLPGKF IILSISY

P1 & 12LZIPC
 PTLSEVKGIVVHRLEAV SYNIGSQEWYTTVPRYIATNGYLISNFDDESSCVFVS

ESAICSQNSL YPMSPLLQQC IRGDTSSCAR TLVSGTMGNK FILSKGNIVA

NCASILCKCY STSTIINQSP DKLLTFLASD TCPLVEIDGA TIQVGGRQYP

LVS Coiled-Coil
ALLMOTI5
P12 & 23LZIPC
 DMVYEGKVAL G *PAISLD *RL*DVGTNLGNALKKLDDAKYLI*

Transmembrane Region
 DSS* NQILETVRRS* SFN *EGSLLSVPILSCTALALLLIYCC*

K RRYQQITLKQH TKVDPAFKPD LTGTSKSYVR SL

FIG. 23

Fusion ♡ALLMOTIS♡
 Peptide ♡107x178x4♡
 ♡.....EIGAI IGSVALGVA TAAQITAASA LIQANQNAAN ♡ILRLKETSTA

 TIEAVIEYTDGLSOLAYA ♡ VG KM ♡ QQFVNDQFNNTAQELDCIKITQQV

 ♡ALLMOTIS♡
 GVELNLYLTELT TV FGPQITSPAL ♡TQLTIQALYNAGGNMDYLLTKLGVG

 ♡P1 & 12LZIPC♡
 NNQLSSLIGSGLIT GN ♡ ♡PILYDSQT QLLGIQVILP SVGNLNNMRATYLET

 LSVST TKG FASALVP KVV TQVGSVI EELDTSYCIE TDL DLYCTRJ VTFPMSPGIY

 SCLNGNTSAC MYSKTEGALT TPYMTLKGSV IANCKMTTCR CADPPGHSQ

 ♡ALLMOTIS♡
 ♡107x178x4♡
 NYGEAVSLID RHSCN ♡ ♡VLSLD GITLRLSGEF DATYQKNISI LDSQVIVTG

 LVS Coiled-Coil ♡Trans-
 NLDISTELGNV NNSISNALDK LEESNSKLDK VNVKLTSTSA ♡LET YIA

 membrane Region ♡
 LTAISLVCGILSLV ♡ ♡ LACYLMY ♡ KQKAQQKTLLWLGNNTLGQMRATTKM

FIG. 24

Fusion ♡ALLMOTI5♡
 Peptide ♡107x178x4♡ *LVS Coiled-Coil*
ETGGY ♡IG ♡TIALG ♡YATSAQITAAVALVEAKQARSDIEKLKE

AIRDTNKAYOSVOSSIGNLIYAIKSVQ* DYVNKE♡ ♡ IVPSIARLGCEAAG

♡ALLMOTI5♡
 ♡107x178x4♡
 LQLGIALTQH ♡♡YSELTNIEGDNIGSLOEKGIKLOGIASLYRTNTE♡ ♡

♡P5 & 12LZIPC♡
 IFTTSTVDKYDIYDLLFTESIKVRVIDVDLNDYSITLQVRL ♡PLLTRLNTQIYR

VDSISYNI♡ QNREWI♡ PLPSHIMTKGAFLGGADVKECIEAFSSYIC

PSDPGFVLNHEMESCLSGNISQCPRTVVKSDIVPRYAFVNGGVVANCITT

TCTCNGIGNRINQPPDQGVKIITHKECNTIGINGMLFNTNKEGTLAFYTP

♡ALLMOTI5♡
 ♡107x178x4♡
 ♡P6 & 23LZIPC♡
 NDITLNNSVALD ♡PIDI ♡SIELN ♡KAKSDLEESKEWI♡ RRSNQIKL♡

♡Transmembrane Region♡
DSIGNWLIQSSTT ♡IIIV♡ LIMHLEHNVTH♡ IIHVKYV♡ R
 IQKRNKRVLDQN DKPYVLINK

FIG. 25

Fusion
Peptide
.....GJFGAI AGFIENGWEGMIDGWYGFRIIQNSEGTG

♣107x178x4♣
▼ALLMOTIS▼
LYS Coiled-Coil
*Q ▼AADLKST ♣QAAIDQINGKLNRYIEKTNEKTHQTEKEEVEGRIQ

DLEKXYEDTKIDL* WSYNAELLVALENQHTI♣ DLT▼ DSEMKNLFETR

RQLRENAEEMGNGCFKIYHKCDNACIESIRNGTYDHDVYRDEALNNRFQIKG

VELKSGYKDWILWISFAISCFLLCVVLLGFIMWACQQRGNIRCNICI

FIG. 26

			FUSION ARRAY	
			PURIFIED	
			IC50 (XTT)	
RSV F2	AV		(μ g/ml)	CD
T-142	++		39	++
T-143	++		31	+++
T-144	+		114	++
T-145	++		40	+
T-146	-		281	-
T-147	-		204	-
T-148	-		354	-
T-149	-		336	-
T-150	-		342	+
T-151	+/-		116	+
T-152	+/-		117	++
T-153	-		280	+
T-154	+/-		118	++
T-155	-		253	+

FIG.27B

RSV	PEPTIDE#	AVG. IC50 (XTT) UG/ML
T-22	I E L S N I K E N K C N G T D A K V K L I K Q E L D K Y K N A V T E L Q L L M Q S T	>500
T-23	I E L S N I K E N K C N G T D A K V K L I K Q E L D K Y	>500
T-24	E N K C N G T D A K V K L I K Q E L D K Y K N A V T E L	>500
T-25	D A K V K L I K Q E L D K Y K N A V T E L Q L L M Q S T	>500
T-26	C N G T D A K V K L I K Q E L D K Y K N A V T E L Q L L	>500
T-27	S N I K E N K C N G T D A K V K L I K Q E L D K Y K N A V T E L Q L L	>500
T-68	V S K G Y S A L R T G W Y T S V I T I E L S N I K E N	165
T-334	A F I R K I S D E L L H N V	26
T-371	Y T S V I T I E L S N I K E N K U N G T D A K V K L I K Q E L D K Y K	>500
T-372	T S V I T I E L S N I K E N K U N G T D A K V K L I K Q E L D K Y K N	NOT TESTED
T-373	S V I T I E L S N I K E N K U N G T D A K V K L I K Q E L D K Y K N A	>500
T-374	S N I K E N K U N G T D A K V K L I K Q E L D K Y K N A V T E L Q L L	>500
T-375	K E N K U N G T D A K V K L I K Q E L D K Y K N A V T E L Q L L M Q S	>500
T-575	A V S K G Y L S A L R T G W Y T S V I T I E L S N I K E N K U N G T D A	>100

FIG.27C

[illegible]

FIG. 27D

			FUSION ASSAY	
			PURIFIED	
	RSV		IC50 XT1	
	F-107	AV	($\mu\text{g/ml}$)	CD
	T-120	-	204	-
	T-121	-	354	-
	T-122	-	347	-
	T-123	+/-	126	-
	T-124	+	95	-
	T-125	+	84	-
	T-126	+	89	-
	T-127	+	89	-
	T-128	-	206	-
	T-129	-	343	-
	T-130	-	177	-
	T-131	+/-	118	-
	T-132	-	272	-
	T-133	+/-	307	-
	T-134	+/-	187	-
	T-135	+	60	-
	T-136	-	194	-
	T-137	+	99	-
	T-138	++	38	-
	T-139	+	86	+/-
	T-140	-	160	+/-
	T-141	-	204	+/-

FIG. 27E

RSV																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																					
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FIG. 27F

[illegible]

FIG. 28A

			FUSION ASSAY PURIFIED	
RSV	AV	IC50		
T-67	++	($\mu\text{g/ml}$) (XIT)	CD	+/-
F1-178		37		
T-104	+	95		
T-105	+	86		
T-106	-	186		
T-107	++	20		
T-108	+++	6		
T-109	+++	8		
T-110	++	30		
T-111	+++	9		
T-112	+++	8		+/-
T-113	+++	6		+/-
T-114	+++	5		+/-
T-115	+++	6		+/-
T-116	+++	9		+/-
T-117	+++	14		+/-
T-118	+++	5		+/-
T-119	+++	6		+/-

FIG.28B

[illegible]

FIG. 28C

[illegible]

FIG. 29A

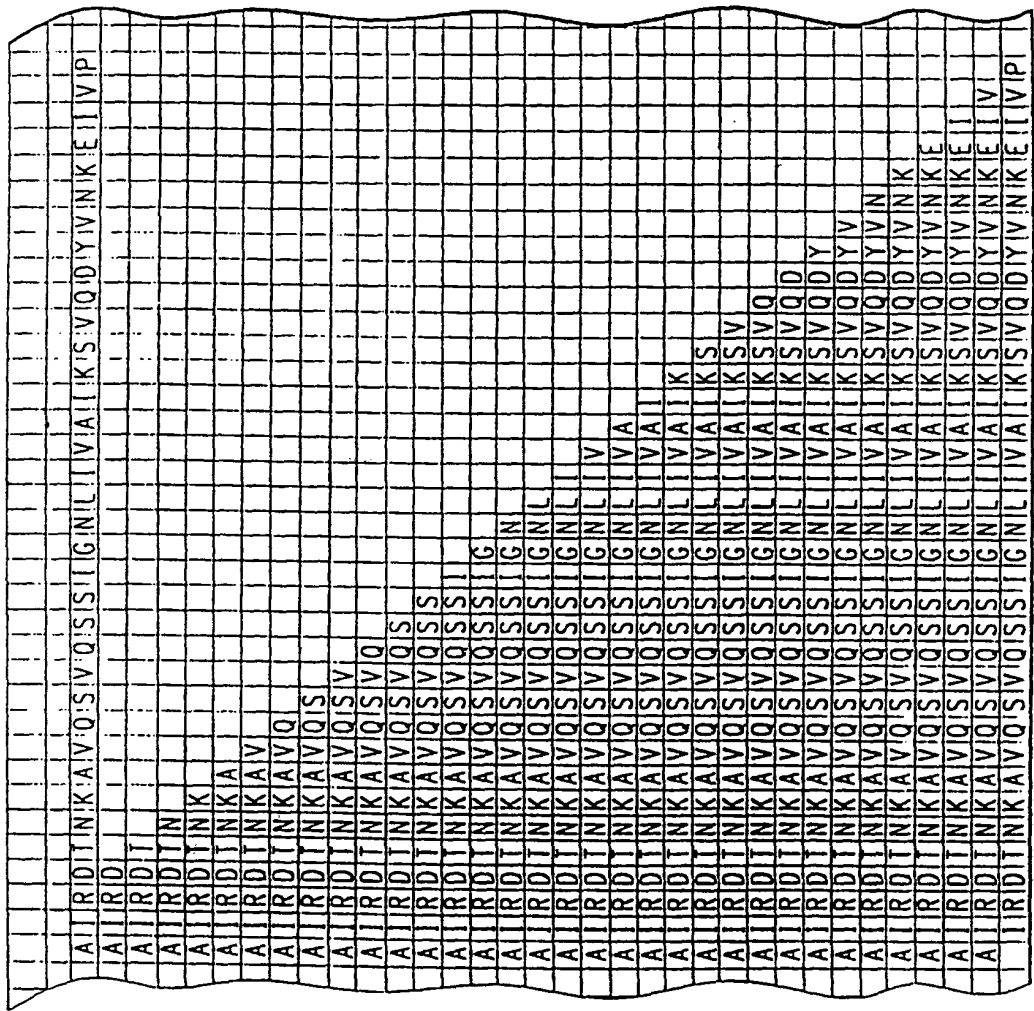


FIG. 29B

HP1V3 107	AV	IC50 (UG/ML)	CO
157	-	574*	+
158	-	146*	+
159	-	707*	+
160	-	536*	+
161	-	390*	+
162	-	403*	+
163	-	123*	+
164	-	512.067*	++
165	-	742*	-
166	-	540*	-
167	-	215*	-
168	-	680*	-
169	-	137*	-
170	-	456*	-
171	-	437*	-
172	+	63*	-
173	++	30*	-
174	+	56*	++
1-40	+/-		+++
175	+/-	110*	++
176	-	197.75*	+++
177	-	350*	+
178	++	30*	+
179	-	295*	-
180	-	732*	-
181	-	929*	-
182	-	707*	-
183	-	218.50*	++
184	+	67.8*	+++
185	-	542*	-
186	-	613*	-
187	-	152*	-
188	-	669*	-

FIG.29C

[illegible]

FIG. 29D

[illegible]

FIG. 29E

[illegible]

FIG. 30A

HP1V3 178	AV	IC50 ($\mu\text{g}/\text{ml}$)	CD
189	-	827*	-
190	-	775*	-
191	-	612*	-
192	-	699*	-
193	-	525*	-
194	+	61*	-
195	+	49	++
196	+++	3.1	+
197	+++	71.15	++
198	+++	0.325	+
199	++	2.3*	+
200	++	1.0*	++
201	+++	0.224*	+
202	+++		+
203	+++	0.390*	+
204	+++	0.213	+
205	+++	0.174	+
206	+++	2.0*	+
207	+++	2.0*	+
208	++	37*	+
209	+++	1.0*	+
210	++	2.0*	+

FIG. 30B

FUSION ♥ALLMOTIS♥
PEPTIDE ♠107x178x4♠
.....RNKRGVFVLGFLGFLATAGSAMGAAS ♠♥ XXXXAQSRTLLAGIVQOOOQ

LLDVVKROQELLRLTVWGTKNLQTRVTAIEKYLKDOAQL♠NAWG♥ CAF

♥ALLMOTIS♥
*LVS PREDICTED COILED-COIL
RQVCITTVWPWPNASLTPDW *NND ♥TWQEWERKVDPLEENITALLEEAQIQQ

♠107x178x4♠
EKNMY ♠ELOKLNSWD* VF♥ GNXXXXXXXXXXXXXXXXXXXXXXXXXXXXX♠

IYIVMLAKLRQGYRPVFSSPPSYFQXTHTQQDPALPTREGKEGDGGEGGGNSSWP
WQIEYIHF

FIG. 31

MTRRRVI.SVVVLLAALACRLGAQTPEQPAPPATTVQPTATRQQTSEFPRVCELSSHGDLFRFSSD

♠ 107x178x4♠

IQCPSEGTRENHTEGLLMVFKDNIIPYSF ♠ KVRSYTKIVTNILYNGHYADSVNTRHE♠

EKFVSUSY LTDQMDTIYQ CYNVAKMTKD GLTRVYVDRD GVNITVNLKP TGGLANGVRR

YASQTELYDA PGWLIWYRT RTTVNCLITD MMAKSNSPFD FFVTTTGQTV EMSPFYDGKN

KETFHERADS FHVRTNYKIV DYDNRGTNPQ GERRAFLDKG TYTLSWKLEN RTAYCPLQHW

QTFDSTIATE TGKSIHFVTD EGTSSFVTNT TVGIELPDAF KCIEEQVNKT HEKYEAVQD

RYTKGQEAIT YFITSGGLLL AWLPLTPRSL ATVKNLTELT TPTSSPPSSP SPPAPSAARG

STPAAVLRRR RRDAGNATTP VPPTAPGKSL GTLNNPATVQ IQFAYDSLRR QINRMLGDLA

RAWCLEQKRQ NMVLRELTKI NPTTVMSSII GKAVAAKRLG DVISVSQCVP VNQATVTLRK

• SMRVPGSETM CYSRPLVSFS FINDTKTYEG QLGTDNEIFL TKKMTEVCQA TSQYYFQSGN

♠ 107x178x4♠

EIIHVYNDYHH FKTJELDGIA TLQTFISLNT ♠ SLIENIDFASLELYSRDEQRASNVED *LE♠

LVS PREDICTED COILED COIL

TM Potential

GIFREYNFQAQNIAGLRKDLDNAVSN* GRNQ FVDGLGELMDSLGSVG QSITN

♣P12LZIPC♣

TM Potential

TM Potential

LVSTVGGLFSSLVSGFISF FK N ♣PFGGMLILVLVAGVVILVISL♣ TRRTRQMS

QQPVQMLYPG IDELAQQHAS GEGPGINPIS KTELQAIMLA LHEQNQEQR AAQRAAGPSV

ASRALQAARDRFPGLRRRRY IIDPEIAALL GEALTEF

FIG. 32

46/85

MMDPNSTSLD VKFTDPYQV PFVQAFDQAT RVYQDLGGPS QAPLPCVLWP VLPEPLPQGQ
L IAYIIVSTAP TGSWFSAPQP APENAYQAYA APQLFPVSDI TONQQTNQAG GEAPQPGDNS
TVQTAAVVVF ACPGANQGQQ LADIGVPQPA PVAAPARRTR KPQQPESLEE CQSELEI
@DNA BINDING@ ♠107x178X4♠ +DIMERIZATION+
@KRY KNRVASRKCRK ♠EK@ Q ♠LLQHYREVAAAKSSENDRLRLLLKQ♠
MCPSLDVD+ SI IPRTPDVLHE DLLNF

FIG. 33

FUSION
 PEPTIDE ♡ALLMOTI5♡ *LVS COILED-COIL*
 FAG ♡VVLAGAALGVATAAQITAGIALHQSM L*NSQAIDNLRASLETTN

QAIEAIRGAGOEMI*LAVQGVQDYINN♡ ELIPSMNQLSCDLIGQKLGLKLLRYYT

♣P23LZIPC♣
 ♣P6,12LZIPC♣
 ♠107X178X4♠
 ♡ALLMOTI5♡
 [II SLFGPSLRD] ♣PISA ♠♡EISIQLSYALGGDINKV♣ LEKLGYSGGDL♣

♣P1,12LZIPC♣
LGILES♠ RGIKARI♡ THVDTESYFIVLSIAY ♣PTLSEIKGVIVHRLEGV♣ SY
 NIGSQEWYTTVPKYVATQGYLISNFDDESSCTFMPEGTVCSONALYPMSPLLQECL
 RGSTKSCARTLVSGSFGNRFILSQGNLIANCASILCKCYTTGTIINQDPDKILTYIAA

♣P23LZIPC♣
 ♣P12LZIPC♣
 ♡ALLMOTI5♡
 LVS COILED-COIL
 DHCPVVEVNGVTIQVGSRRYPDAVYLHRIDLGP ♣P ♡IS *LERLDVGTNLGN

♦TRANSMEMBRANE REGION♦
AIKLEDAKELL♣ ESSDOI*L♣ RSMK ♦GLSSTSIVYILI♡ AVCLGGLIGIP
ALICCC♦ RGRCNKKGEQVGMSPGLKPDLTGTSKSYVRS L

FIG. 34

Pre S1 and Pre S2

MGQNLSTSNPLGFFPDIIQLDPAFRANTANPDWDFNPNKDTWPDANKVGAGAFG

LGFTPIHGGLLGWSPQAQGILQTLPANPPPASTNRQSGRQPTPLSPPLRNTIIPQAM

QWNSTTFHIQTLQDPRVRGLYFPAGGSSSGTVNPVLTITASPLSSIFSRIGDPALN

MAJOR SURFACE ANTIGEN(HBs)

FUSION

PEPTIDE

♣P12 & 23LZIPC♣

MENITSG FLG ♣PLL VI.QAGFFLLTRILTI♣ PQSLDSWWTSNLFLGGTTVCLG

♣P12 & 23LZIPC♣

QNSQSPTSNHSPTSCPPTC ♣PGYRWMCLRRFIHFLFILLCLIFLLVLLDYQGML♣

PVCPLIPGSSTTSTGPCRTCMTTAQGTSMYPSCCCTKPSDGNCTCIPSSWAFGKF

♦TRANSMEMBRANE REGION♦

LWEWASARFSWLS ♦LLVPFVQWFVGLSPTVWLSVI♦ WMMWYWGPSL

♦TRANSMEMBRANE REGION♦

♦YSILSPFLPLLPIFFCLWVYI♦

FIG. 35

FUSION ♥ ALLMOTIS ♥ ♠107x178x4♠
PEPTIDE *LVS COILED COIL
AIQIIPLFVG LGI ♥TTAVSTGAAGLGVS ♠IT *QYTKLSHOLISDV
QAISSTIODLODOVDSLAEVVLO* NRRGLDLLTAE♠ QGGI♥
CIAIQEKCCFYANKSGIVRDKIKNLQDDLERRRRQLIDNPFWTSFHG
FILPYVMPLLGPLLCLLLVLSFGPIIFNKLMTFIKHQIESIQAKPIQVHYII
TRANSMEMBRANE REGION
RLEQEDSGGSYLTLT.....??????????????????????????...

FIG. 36

MKAQKGFTLI ELMIVVAHG ILAAIAPGQ

♠107x178x4♠

♥ALLMOTI5♥

♠♥YODYTARTOVTRAVSEVSALKTAAESAILEGKEIVSSA♠ T♥

PK DTQYDIGFT

♠107x178x4♠

♥ALLMOTI5♥

♠♥ESTLLDGSGKSOIQVTDNODGTVELVATLGKSSGS♠ AIKGAVITSR♥

KNDGV WNCKITKTPT AWKPNYAPAN CPKS

FIG. 37

MNTLQKGFTL IELMIVIAIV GILAAVALPA YQDYTARAQV

SEAILLAEGQ KSAVTEYYLN HGIWP

♣107x178x4♣

♥ALLMOTIS♥

♣♥KDNTSAGVASSSSIKGKYVKEVKVENGVVAT♣

MNSSNVNKEIQGKKLSLWAKRQDGSVKW♥

FCCQP VTRNAKDDTV TADATGNDGK IDTKHLPSTC RDNFDAS

FIG. 38

MKKTLLGSLI LLAFAAGNVQA DINTETSGKV TFFGKVVENT

CKVKTEIIKNL SVVLNDVGKN SLSTKVNTAM PTPFTITLQN

CDPTTANGTA NKANKVGLYF Y

♠107x178x4♠

♥ALLMOTI5♥

♠♥SWKNYDKENNETLKNEOTTADYATNVNI♠

QLMESNGTKAISVVGKETE♥

DF MHTNNNGVAL NQTHPNNNAHI SGSTQLTTGT NELPLHFIAQ

YYATNKATAG KVQSSVDFQI AYE

FIG. 39

MNKKLLMNF IVSPLLLATT ATDFTPVP

♠107x178x4♠

♥ALLMOTI5♥

♠♥LSSNOIHK TAKASTNDNIKDLLDWYSSGSDTFTNS♠♥

EVLDNSL GSMRIKNTDG SISLIIFPSP YYSPAFTKGE KV

♠107x178x4♠

♠DLNTKRTKKSQIITSEGTYIHFOISGVT♠

N TEKLPTPIEL PLKVKVHGD SPLKYG

♣P12LZIPC♣

♣PKFDKKQLAISTLDFEIRHQLTQI♣

IIGLYRSSDKT GGYWKITMND GSTYQSDLSK KFEYNTEKPP

INIDEIKTIE AEIN

FIG. 40

♥ALLMOTI5♥
 MKKTAFILLL FIALTLTTSP L ♥VNG

♠107x178x4♠
 LVS PREDICTED COILED-COIL
 S ♠EKSEEINEKDLRKKSELORNALSNLROIY YYNEKAITENKESDD♠

QFLENTLL♥FKG FFTGIIPW

♠107x178x4♠
 ♠YNDLLVDLGSKDATNKYKGKKVDLYGAY♠

YGYQCAGGTPNKTACMYGGVTLIIDN NRLTEKKVP INLWIDGKQTTV

♣P12LZIPC♣
 ♣PIDKVKTSKKEVTVQELDL♣ QARIHYLHGK FGLYNSDSFGGKVQ

♣P12LZIPC♣
 RGLIVF IISSEGSTVS Y DLFDAQQY ♣P DTLLRIYRDN KTINSENLHI♣

DLYLYTT

FIG. 41

♥ALLMOTI5♥
MKKTAFTLLL FIALTLTTSP L ♥VNGS

♠107x178x4♠
♠EKSEEINEKDLRKKSELOGTALGNLKOIYYYNEKAKTENKESHD♠ Q♥

FLQHTILFKG FFTDIISWYND LLVDFDSKDI VDKYKGKKVDLYGAYY

GYQC AGGTPNKTAC MYGGVTLIIDN NRLTEKKVPINL WLDGKQNTV

♠107x178x4♠
♥ALLMOTI5♥
♣P12LZIPC♣
♣P ♥L ♠ETVKTNKKNVTVOELDLOARRYL♣ OEKYNLYN♠

SDVFDGKVQR♥ GLIVF HTSTE

♣P23LZIPC♣
♣PSVNYDLFGAQQQYSNTLLRIYRDNKTINSENMIH♣ DIYLYTS

FIG. 42

MKNITFIFFILLASPLYANGDRLYRADSRPPDEIKRFRSLMPRGNEYFDRGT

♥ALLMOTIS♥
♥QMNLNLYDHARGTQTGFVRYDDGYV

♠107x178x4♠
♠STSLSLRSAHLA GOYILSGYSLTIYIVI♠ ANMFNVNDVISVY♥

SP HPYEQEVSA L GGIPYSQIYG WYRVNFGVID ERLHRNREYR

DRYYRNLNIA PAEDGYRLAG FPPDHQAWRE EPWIHHAPQG

CGDSSRTITG DTCNE

♥ALLMOTIS♥
♥ETQNLSTIYLR EYQSKVKRQIFSDYQSEVDIYNRIRDEL♥

FIG. 43

MMFSGFNADY EASSSRCSSA SPAGDSLSYY HSPADSFSSM
GSPVNAQDFC TDLAVSSANF IPTVTAISTS PDLQWLVPQA
LVSSVAPSQT RAPIIPFGVPA PSAGAYSRAG VVK'TMTGGRA

LVS PREDICTED COILED-COIL
QSIGRRGKVE QLSPEEEER RIRRE *RNKMA AAK

♣107x178x4♣

♥ALLMOTIS♥

♥CRNRRREL ♣TDTLOAETDOLEDEKSALOTEIANLLKEKEKL♥

EFILAAHR* PACKIPDDL GFPEEMSVAS LDLTGGLPEV
ATPESEEAFT LPLLNDPEPK PSVEPVKIS SMELKTEPFD
DFLFPASSRP SGSETARSVP DMDLSGSFYA LPLLNDPEPK
PSVEPVKIS SMELKTEPFD DFLFPASSRP SGSETARSVP
DMDLSGSFYA GSSSNPSSD SLSSPTLLAL

FIG. 44

SGWESYYKTEGDEEAEEEEQEENLEASGDYKYSGRDSLIFLVDASKA
 MFESQSEDELTPFDMSIQCIQSVYISKIISDRDLLAVVFGTEKDKNS
 VNFKNYVLQELDNPGAKRII.ELDQFKGQQGQKRFQDMMGHGSDY
 SLSEVLWVCANLFSQVQFKMSHKRIMLFTNEDNPHGNDASAKSRAR
 TKAGDLRDTGIFLDMHLKKPGGFDISLFYRDIISIAEDED

♠107x178x4♠

♥ALLMOTIS♥

LVS PREDICTED COILED-COIL

♥LRVH *FEE ♠SSKLEDLLRKVRKETRKRALSRLKLKLNKDIV* ISV

GIYNLVQKAL♥ KPPPIKLYRETN♠ EPVKTKTRTFNTSTGGLLLPSDTKR

SQIYGSRQIILEKEETEELKRFDGPGLMLMGFKPLVLLKKHHLRPSLFVYPE
 ESLVIGS STLFSALLIKCLEKEVAALCRYTPRRNIPPYFVALVPQEEELDDQK
 IQVTPPGFQLVFLPFADDKRKMPFTEKIMATPEQVGKMKAIKELRFTYRS
 DSEFNPNVLQQIIFRNLEALALDLME

♣PI2LZIPC♣

♣PEQAVDLTLPKVEAMNKRL♣ GSLVDEFKELVYPPDYNPEGKVTKR
 KHDNEGSGSKRPKVEYSEEELKTHISKGTGKFTVPMLKEACRAYGLKSG
 LKKQELLEALTKHFQD

FIG. 45

GGGALSPQHSAVTQGSIIKNKEGMDAKS

♠107x178x4♠

♥ALLMOTIS♥

♥♠LTAWSRTLYTEKDVFEVDFREEWKLLDT♠ AQQIVYRNV
MLENYKNLVSLGYQLT♥ KPDVILRLEKGEEPWLVEREIHQETHPD
SETAFEIKSSVSSRSIFKDKQSCDIKMEGMARNDLWYLSLEEVWKC
DQLDKYQENPERIILRHQLIITGEKPYECKEKGKSFSSSHLIGHQKT
IITGEEPYECKEKGKSFWSHVLVTHQRTHTGDKLYTCNQCGKSFVH
SSRLIRHQRTHTGHKPYECPECKGKSFQSTHLILHQRTHVVRVPYECN
ECKSYSQSRSHLVVHHRIHTGLKPFECKDCGKCFSSSHLYSHQRT
TGEKPYECHDCGKSFSQSSALIVHQRIHTGEKPYECCQCGKAFIRKN
DIJKIQRHIVGAIETYKCNQCGHIFSQNS

♣P23LZIPC♣

♣PFIVHQIAHTGEQFLTCGNQCGTALVNTSNLIGQTNHI♣ RENAY

FIG. 46

[illegible]

FIG. 47A

	AVERAGE		CD
	IC50		
	-		-
	-		-
	-		-
	-		-
	-		-
	-		-
	1.35ug/ml		-
	.343ug/ml		-
	1.78ug/ml		-
	.186ug/ml		-
	+		-
	.193ug/ml		-
	1.32ug/ml		-
	1.01ug/ml		-
	.072ug/ml		-
	-		-
	+/-		-
	+		-

FIG. 47B

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FIG. 48A

HIV-1 BRU WALKS N-TERMINAL TO DP178									
		AA#							
		6		6	6	6	6	6	6
		1	11	2	2	2	2	2	2
		5		3	3	3	3	3	3
				4	4	4	4	4	4
				5	5	5	5	5	5
				6	6	6	6	6	6
				7	7	7	7	7	7
				8	8	8	8	8	8
				9	9	9	9	9	9
				10	10	10	10	10	10
				11	11	11	11	11	11
				12	12	12	12	12	12
				13	13	13	13	13	13
				14	14	14	14	14	14
				15	15	15	15	15	15
				16	16	16	16	16	16
				17	17	17	17	17	17
				18	18	18	18	18	18
				19	19	19	19	19	19
				20	20	20	20	20	20
				21	21	21	21	21	21
				22	22	22	22	22	22
				23	23	23	23	23	23
				24	24	24	24	24	24
				25	25	25	25	25	25
				26	26	26	26	26	26
				27	27	27	27	27	27
				28	28	28	28	28	28
				29	29	29	29	29	29
				30	30	30	30	30	30
				31	31	31	31	31	31
				32	32	32	32	32	32
				33	33	33	33	33	33
				34	34	34	34	34	34
				35	35	35	35	35	35
				36	36	36	36	36	36
				37	37	37	37	37	37
				38	38	38	38	38	38
				39	39	39	39	39	39
				40	40	40	40	40	40
				41	41	41	41	41	41
				42	42	42	42	42	42
				43	43	43	43	43	43
				44	44	44	44	44	44
				45	45	45	45	45	45
				46	46	46	46	46	46
				47	47	47	47	47	47
				48	48	48	48	48	48
				49	49	49	49	49	49
				50	50	50	50	50	50
				51	51	51	51	51	51
				52	52	52	52	52	52
				53	53	53	53	53	53
				54	54	54	54	54	54
				55	55	55	55	55	55
				56	56	56	56	56	56
				57	57	57	57	57	57
				58	58	58	58	58	58
				59	59	59	59	59	59
				60	60	60	60	60	60
				61	61	61	61	61	61
				62	62	62	62	62	62
				63	63	63	63	63	63
				64	64	64	64	64	64
				65	65	65	65	65	65
				66	66	66	66	66	66
				67	67	67	67	67	67
				68	68	68	68	68	68
				69	69	69	69	69	69
				70	70	70	70	70	70
				71	71	71	71	71	71
				72	72	72	72	72	72
				73	73	73	73	73	73
				74	74	74	74	74	74
				75	75	75	75	75	75
				76	76	76	76	76	76
				77	77	77	77	77	77
				78	78	78	78	78	78
				79	79	79	79	79	79
				80	80	80	80	80	80
				81	81	81	81	81	81
				82	82	82	82	82	82
				83	83	83	83	83	83
				84	84	84	84	84	84
				85	85	85	85	85	85
				86	86	86	86	86	86
				87	87	87	87	87	87
				88	88	88	88	88	88
				89	89	89	89	89	89
				90	90	90	90	90	90
				91	91	91	91	91	91
				92	92	92	92	92	92
				93	93	93	93	93	93
				94	94	94	94	94	94
				95	95	95	95	95	95
				96	96	96	96	96	96
				97	97	97	97	97	97
				98	98	98	98	98	98
				99	99	99	99	99	99
				100	100	100	100	100	100

FIG. 49A

[illegible]

FIG. 49B

[illegible]

FIG. 49C

[illegible]

FIG. 49D

HIV-1 BRU	CONSTRUCTS,	MUTATIONS,	TRUNCATIONS
T4	X		Y T S L I H S L I E E S Q N Q Q E K NO NHZ
T28	X		Y T S L I H S L I E E S Q N Q Q E K
T700			Y T S L I H S L I E E S Q N Q Q E K NEQE L
T715	X		T S L I H S L I E E S Q N Q Q E K NEQE L
T65/T716	X		L I H S L I E E S Q N Q Q E K NEQE L
T714	X		L I H S L I E E S Q N Q Q E K NEQE L
T712	X		L I E E S Q N Q Q E K NEQE L
T64	X		E S Q N Q Q E K NEQE L
T63	X		NQ QEK NEQE L
T62	X		E K NEQE L
T3	X	X	NO AC - NEQE L
T61/T102	X		N EQE L
T217	X		EQE L
T218	X		EQE L
T219	X		E L E L D K W A S L

FIG. 49E

[illegible]

FIG. 49F

T220	X										L	E	L	D	K	W	A	S	L	W	N	W	F
T221	X										L	E	L	D	K	W	A	S	L	W	N	W	F
T234	X										E	A	A	R	E	A	A	R	E	A	A	R	E
T235	X										R	M	K	Q	L	E	D	K	V	E	E	L	S
T570	X										F	W	N	W	L	S	A	W	K	D	L	E	L
T381	X										R	M	K	Q	L	E	D	K	V	E	E	L	S
T382	X										K	V	E	E	L	S	K	N	Y	H	L	E	N
T677	X										F	W	N	W	L	S	A	W	K	D	L	E	L
T376	X										C	L	E	D	K	W	A	S	L	W	N	W	F
T589	X										C	L	E	D	K	W	A	S	L	W	N	W	F
T377	X										C	L	E	D	K	W	A	S	L	W	N	W	F
T590	X										C	L	E	D	K	W	A	S	L	W	N	W	F
T378	X										C	L	E	D	K	W	A	S	L	W	N	W	F
T591	X										C	L	E	D	K	W	A	S	L	W	N	W	F
T270	X										L	E	L	D	K	W	A	S	L	W	N	W	F
T271	X										L	E	L	D	K	W	A	S	L	W	N	W	F
T272	X										L	E	L	D	K	W	A	S	L	W	N	W	F
T273	X										L	E	L	D	K	W	A	S	L	W	N	W	F
T608	X										L	E	L	D	K	W	A	S	L	W	N	W	F
T609	X										L	E	L	D	K	W	A	S	L	W	N	W	F
T610	X										L	E	L	D	K	W	A	S	L	W	N	W	F
T611	X										L	E	L	D	K	W	A	S	L	W	N	W	F
T612	X										L	E	L	D	K	W	A	S	L	W	N	W	F
T222	X										L	E	L	D	K	W	A	S	L	W	N	W	F
T223	X										L	E	L	D	K	W	A	S	L	W	N	W	F
T60/T224	X										L	E	L	D	K	W	A	S	L	W	N	W	F
T225	X										L	E	L	D	K	W	A	S	L	W	N	W	F
T226	X										L	E	L	D	K	W	A	S	L	W	N	W	F
T227	X										L	E	L	D	K	W	A	S	L	W	N	W	F

FIG. 49G

T220	59000
T221	16000
T234	>100000
T235	53000
T570	>100000
T381	89000
T382	190000
T677	6310
T376	>100000
T589	745000
T377	69000
T590	30290
T378	95000
T591	59000
T270	>200000
T271	16000
T272	1000
T273	>100000
T608	>100000
T609	>100000
T610	>100000
T611	70000
T612	>100000
T222	49000
T223	57000
T60/T224	77000
T225	>100000
T226	>100000
T227	>100000

FIG. 49H

[illegible]

FIG. 49J

T99	X										Y	T	S	L	I	H	S	L	I	E	E	S
T103	X										Y	T	S	L	I	Q	S	L	I	E	E	S
T212	X										Y	T	S	L	I	H	S	L	I	E	E	S
T213	X										Y	T	S	L	I	H	S	L	I	E	E	S
T214	X										Y	T	S	L	I	H	S	L	I	E	Q	S
T215	X										Y	T	S	L	I	H	S	L	I	Q	E	S
T216	X										Y	T	S	L	I	H	S	L	I	Q	Q	S
T229	X										Y	T	S	L	I	H	S	L	I	E	E	S
T230	X										Y	T	S	L	I	H	S	L	I	E	E	S
T231	X										Y	T	S	L	I	Q	S	L	I	E	E	S
T379	X										Y	T	S	L	I	H	S	L	I	E	E	S
T701	X										Y	T	S	L	I	H	S	L	I	E	E	S
T702	X										Y	T	S	L	I	H	S	L	I	E	E	S
T703	X										Y	T	S	L	I	H	S	L	I	E	E	S
T704	X										Y	T	S	L	I	H	S	L	I	E	E	S
T705	X										Y	T	S	L	I	H	S	L	I	E	E	S
T706	X										Y	T	S	L	I	H	S	L	I	E	E	S
T156	X										L	D	N	F	E	S	T	W	E	Q	S	
T89	X										L	D	N	F	E	S	T	W	E	Q	S	
T90	X										L	S	N	L	Q	I	S	N	N	S	D	

FIG. 49K

Q	N	Q	Q	E	K	N	Q	Q	E	L	L	Q	L	D	K	W	A	S	L	W	N	W	F	T	9	9	5	6						
Q	N	Q	Q	E	K	N	Q	Q	E	L	L	E	L	D	K	W	A	S	L	W	N	W	F	T	1	0	3	N	D					
Q	Q	Q	Q	E	K	N	Q	Q	E	L	L	E	L	D	K	W	A	S	L	W	N	W	F	T	2	1	2	3						
Q	N	Q	Q	E	K	N	Q	Q	E	L	L	E	L	N	K	W	A	S	L	W	N	W	F	T	2	1	3	2	5					
Q	N	Q	Q	E	K	N	Q	Q	E	L	L	E	L	D	K	W	A	S	L	W	N	W	F	T	2	1	4	1	9					
Q	N	Q	Q	E	K	N	Q	Q	E	L	L	E	L	D	K	W	A	S	L	W	N	W	F	T	2	1	5	2	3					
Q	N	Q	Q	E	K	N	Q	Q	E	L	L	Q	L	D	K	W	A	S	L	W	N	W	F	T	2	1	6	1	0	0				
Q	N	Q	Q	E	K	N	Q	Q	E	L	L	E	L	D	K	W	A	S	L	A	N	A	T	2	2	9	>	1	0	0	0	0		
Q	N	Q	Q	E	K	N	Q	Q	E	L	L	E	L	D	K	E	A	S	L	W	N	W	F	T	2	3	0	6						
Q	N	Q	Q	E	K	N	Q	Q	E	L	L	E	L	D	K	W	A	S	L	W	N	W	F	T	2	3	1	4						
Q	N	Q	Q	E	K	N	Q	Q	E	L	L	E	L	D	K	W	A	S	L	F	N	F	T	3	7	9	0	3						
Q	N	L	Q	E	K	N	Q	Q	E	L	L	E	L	D	K	W	A	S	L	W	N	W	F	T	7	0	1	3						
Q	N	Q	Q	E	K	L	E	Q	E	L	L	E	L	D	K	W	A	S	L	W	N	W	F	T	7	0	2	3	6					
Q	N	Q	Q	E	K	N	Q	Q	E	L	L	E	F	D	K	W	A	S	L	W	N	W	F	T	7	0	3	0	5					
Q	N	Q	Q	E	K	N	Q	Q	E	L	L	E	L	D	K	P	A	S	L	W	N	W	F	T	7	0	4	5	1					
Q	N	Q	Q	E	K	N	Q	Q	E	L	L	E	L	D	K	W	A	S	P	W	N	W	F	T	7	0	5	1	4					
Q	N	Q	Q	E	K	N	Q	Q	E	L	L	E	L	D	K	W	A	S	L	W	N	S	F	T	7	0	6	6	8					
K	E	L	W	E	Q	Q	E	I	S	I	Q	N	L	H	K	S	A	L	Q	E	Y	W	N	T	1	5	6	8	0	0	0			
K	E	L	W	E	Q	Q	E	I	S	I	Q	N	L	H	K	S	A	L	Q	E	Y	W		T	8	9	>	1	0	0	0			
E	W	L	E	A	L	E	I	E	H	E	K	W	K	L	T	Q	W	Q	S	Y	E	Q	F	T	9	0	>	1	0	0	0			

FIG.49L

[illegible]

FIG. 50A

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[illegible]

FIG. 50B

[illegible]

FIG. 51A

[illegible]

FIG. 51B

RESIDUE	197	L	Q	H	Y	R	E	V	A	A	K	S	S	E	N	D	R	L	R	L	L	K	Q	M	C	P	S	L	D	V	D	S	I	I	P	R	T	P	D	V	L	H	E	D		242		45																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																												
T-447	197	L	Q	H	Y	R	E	V	A	A	K	S	S	E	N	D	R	L	R	L	L	K	Q	M	C	P	S	L	D	V	D	S	I	I										232		35																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																														
T-448	198	Q	H	Y	R	E	V	A	A	K	S	S	E	N	D	R	L	R	L	L	L	K	Q	M	C	P	S	L	D	V	D	S	I	I	P									233		35																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																														
T-449	199	H	Y	R	E	V	A	A	K	S	S	E	N	D	R	L	R	L	L	L	L	K	Q	M	C	P	S	L	D	V	D	S	I	I	P	R									234		35																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																													
#	200	Y	R	E	V	A	A	K	S	S	E	N	D	R	L	R	L	L	L	L	L	K	Q	M	C	P	S	L	D	V	D	S	I	I	P	R	T								235		35																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																													
T-451	201	R	E	V	A	A	K	S	S	E	N	D	R	L	R	L	L	L	L	L	L	K	Q	M	C	P	S	L	D	V	D	S	I	I	P	R	T	P							236		35																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																													
T-452	202	E	V	A	A	K	S	S	E	N	D	R	L	R	L	L	L	L	L	L	L	K	Q	M	C	P	S	L	D	V	D	S	I	I	P	R	T	P	D						237		35																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																													
T-453	203	V	A	A	K	S	S	E	N	D	R	L	R	L	L	L	L	L	L	L	L	K	Q	M	C	P	S	L	D	V	D	S	I	I	P	R	T	P	D	V					238		35																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																													
T-454	204	A	A	K	S	S	E	N	D	R	L	R	L	L	L	L	L	L	L	L	L	K	Q	M	C	P	S	L	D	V	D	S	I	I	P	R	T	P	D	V	L					239		35																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																												
T-455	205	A	A	K	S	S	E	N	D	R	L	R	L	L	L	L	L	L	L	L	L	K	Q	M	C	P	S	L	D	V	D	S	I	I	P	R	T	P	D	V	L	H					240		35																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																											
T-456	206	A	K	S	S	E	N	D	R	L	R	L	L	L	L	L	L	L	L	L	L	K	Q	M	C	P	S	L	D	V	D	S	I	I	P	R	T	P	D	V	L	H	E					241		35																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																										
T-457	207	K	S	S	E	N	D	R	L	R	L	L	L	L	L	L	L	L	L	L	L	K	Q	M	C	P	S	L	D	V	D	S	I	I	P	R	T	P	D	V	L	H	E	D					242		35																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																									
T-458	208	S	S	E	N	D	R	L	R	L	L	L	L	L	L	L	L	L	L	L	L	K	Q	M	C	P	S	L	D	V	D	S	I	I	P	R	T	P	D	V	L	H	E	D	L					243		35																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																								

FIG.51C

DOMAIN I:

174 P-L-L-L-V-L-Q-A-G-F-F-L-L-L-T-R-I-L-I-P-Q-S-L-D-S-W-W-T-S-L-N-F-L-G-G-G-T-T-V-C-L-G-Q-N-S-Q-S-P 220

P-L-L-L-V-L-Q-A-G-F-F-L-L-L-T-R-I-L-I-P-Q-S-L-D-S-W-W-T-S-L-N-F-L-G-G-T
L-L-L-V-L-Q-A-G-F-F-L-L-L-T-R-I-L-I-P-Q-S-L-D-S-W-W-T-S-L-N-F-L-G-G-T-T
L-L-L-V-L-Q-A-G-F-F-L-L-L-T-R-I-L-I-P-Q-S-L-D-S-W-W-T-S-L-N-F-L-G-G-T-T-V
V-L-L-Q-A-G-F-F-L-L-L-T-R-I-L-I-P-Q-S-L-D-S-W-W-T-S-L-N-F-L-G-G-T-T-V-C
L-L-L-Q-A-G-F-F-L-L-L-T-R-I-L-I-P-Q-S-L-D-S-W-W-T-S-L-N-F-L-G-G-T-T-V-C-L
Q-A-G-F-F-L-L-L-T-R-I-L-I-P-Q-S-L-D-S-W-W-T-S-L-N-F-L-G-G-T-T-V-C-L-G
A-G-F-F-L-L-L-T-R-I-L-I-P-Q-S-L-D-S-W-W-T-S-L-N-F-L-G-G-T-T-V-C-L-G-Q
G-F-F-L-L-L-T-R-I-L-I-P-Q-S-L-D-S-W-W-T-S-L-N-F-L-G-G-T-T-V-C-L-G-Q-N
F-F-L-L-L-T-R-I-L-I-P-Q-S-L-D-S-W-W-T-S-L-N-F-L-G-G-T-T-V-C-L-G-Q-N-S
F-L-L-L-T-R-I-L-I-P-Q-S-L-D-S-W-W-T-S-L-N-F-L-G-G-T-T-V-C-L-G-Q-N-S-Q
L-L-L-T-R-I-L-I-P-Q-S-L-D-S-W-W-T-S-L-N-F-L-G-G-T-T-V-C-L-G-Q-N-S-Q-S

FIG.52A

DOMAIN II:

223 P-G-Y-R-W-M-C-L-R-R-F-I-I-F-L-F-I-L-L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V-C-P-L-I-P-G-S-S-I-S-I-G-P-C-R-I-C-M-I-I-291

P-G-Y-R-W-M-C-L-R-R-F-I-I-F-L-F-I-L-L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L

G-Y-R-W-M-C-L-R-R-F-I-I-F-L-F-I-L-L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P

Y-R-W-M-C-L-R-R-F-I-I-F-L-F-I-L-L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V

R-W-M-C-L-R-R-F-I-I-F-L-F-I-L-L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V-C

W-M-C-L-R-R-F-I-I-F-L-F-I-L-L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V-C-P

M-C-L-R-R-F-I-I-F-L-F-I-L-L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V-C-P-L

C-L-R-R-F-I-I-F-L-F-I-L-L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V-C-P-L-I

L-R-R-F-I-I-F-L-F-I-L-L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V-C-P-L-I-P

R-R-F-I-I-F-L-F-I-L-L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V-C-P-L-I-P-G

R-F-I-I-F-L-F-I-L-L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V-C-P-L-I-P-G-S

F-I-I-F-L-F-I-L-L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V-C-P-L-I-G-G-S-S

I-I-F-L-F-I-L-L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V-C-P-L-I-P-G-S-S-I

I-F-L-F-I-L-L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V-C-P-L-I-P-G-S-S-I-S

F-L-F-I-L-L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V-C-P-L-I-P-G-S-S-I-S-I

L-F-I-L-L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V-C-P-L-I-P-G-S-S-I-S-I-G

F-I-L-L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V-C-P-L-I-P-G-S-S-I-S-I-G-P

I-L-L-L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V-C-P-L-I-P-G-S-S-I-S-I-G-P-C

L-L-L-L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V-C-P-L-I-P-G-S-S-I-S-I-G-P-C-R

L-L-L-L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V-C-P-L-I-P-G-S-S-I-S-I-G-P-C-R-I

L-L-L-L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V-C-P-L-I-P-G-S-S-I-S-I-G-P-C-R-I-C

C-L-I-F-L-L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V-C-P-L-I-P-G-S-S-I-S-I-G-P-C-R-I-C-M

L-I-F-L-L-L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V-C-P-L-I-P-G-S-S-I-S-I-G-P-C-R-I-C-M-I

I-F-L-L-L-L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V-C-P-L-I-P-G-S-S-I-S-I-G-P-C-R-I-C-M-I-I

FIG.52B

		Fusion IC50 µg/ml	T888 IC50 Conc. (nM)
T112	AC-VFPSDEFDASISQVNEKINQSLAFIRKSDLLHNV-NH2	0.30	1
T800	AC-AAASDEFDASISQVNEKINQSLAFIRKSDLLHNV-NH2	2.6	6.4
T801	AC-VFPAAAFDASISQVNEKINQSLAFIRKSDLLHNV-NH2	1.7	Insoluble
T802	AC-VFPSDEAAASISQVNEKINQSLAFIRKSDLLHNV-NH2	3	75.6
T803	AC-VFPSDEFDAAAQVNEKINQSLAFIRKSDLLHNV-NH2	2.1	7.3
T804	AC-VFPSDEFDASISAAAEKINQSLAFIRKSDLLHNV-NH2	1.3	28.7
T805	AC-VFPSDEFDASISQVNAANQSLAFIRKSDLLHNV-NH2	2.1	
T806	AC-VFPSDEFDASISQVNEKIAAALAFIRKSDLLHNV-NH2	0.9	3.5
T807	AC-VFPSDEFDASISQVNEKINQSAALIRKSDLLHNV-NH2	0.5	195
T808	AC-VFPSDEFDASISQVNEKINQSLAFIRKSDLLHNV-NH2	0.5	7.2
T809	AC-VFPSDEFDASISQVNEKINQSLAFIRKAAALLHNV-NH2	3.8	Insoluble
T810	AC-VFPSDEFDASISQVNEKINQSLAFIRKDEAAANV-NH2	1.3	624
T811	AC-VFPSDEFDASISQVNEKINQSLAFIRKDELLAAA-NH2	1.6	4.8
T1669	AC-VFPSDEADASISQVNEKINQSLAFIRKSDLLHNV-NH2		
T1670	AC-VFPSDEFAASISQVNEKINQSLAFIRKSDLLHNV-NH2		
T1671	AC-VFPSDEFDASISAVNEKINQSLAFIRKSDLLHNV-NH2		
T1672	AC-VFPSDEFDASISQANEKINQSLAFIRKSDLLHNV-NH2		
T1673	AC-VFPSDEFDASISQVAEKINQSLAFIRKSDLLHNV-NH2		
T1680	AC-VFPSDEFDASISQVNEKINQSAALIRKSDLLHNV-NH2		
T1681	AC-VFPSDEFDASISQVNEKINQSLAFIRKSDLLHNV-NH2		
T1682	AC-VFPSDEFDASISQVNEKINQSLAFIRKSDLLHNV-NH2		
T1683	AC-VFPSDEFDASISQVNEKINQSLAFIRKSDLLHNV-NH2		
T1684	AC-VFPSDEFDASISQVNEKINQSLAFIRKSDLLANV-NH2		

FIG. 53

		Does Substitution prevent CD interaction?	Fusion IC50 (ng/mL)	T83 ELARA (Biot-T20) IC50 Conc. (nM)	T1342 FP (Fluo-T20) IC 50 Conc. (nM)
T20	Ac-YTSLIHSIIIESQSQKNEQELLELDKWSLWVWF-NH2	Native	2	69	
T813	Ac-AAAIIHSIIIESQSQKNEQELLELDKWSLWVWF-NH2		3	1000	
T878	Ac-YTSAASIIIESQSQKNEQELLELDKWSLWVWF-NH2	Reduced	37	1000	
T877	Ac-YTSLIAAASIIIESQSQKNEQELLELDKWSLWVWF-NH2	Inhibited	1757	Neg	
T876	Ac-YTSLIHSIIIAAQNQQKNEQELLELDKWSLWVWF-NH2	Native	11	29	
T875	Ac-YTSLIHSIIIESAAQKNEQELLELDKWSLWVWF-NH2	Inhibited	33	>3000	
T874	Ac-YTSLIHSIIIESQQAANEQELLELDKWSLWVWF-NH2	Inhibited	545	>3000	
T873	Ac-YTSLIHSIIIESQQAEEAELLELDKWSLWVWF-NH2	Inhibited	814	Neg	
T872	Ac-YTSLIHSIIIESQQAEEAELLELDKWSLWVWF-NH2	Native	23	66	
T871	Ac-YTSLIHSIIIESQQAEEAELLELDKWSLWVWF-NH2	Inhibited	89	1156	
T870	Ac-YTSLIHSIIIESQQAEEAELLELDKWSLWVWF-NH2	Reduced	8	251	
T869	Ac-YTSLIHSIIIESQQAEEAELLELDKWSLWVWF-NH2	Reduced	28	57	
T868	Ac-YTSLIHSIIIESQQAEEAELLELDKWSLWVWF-NH2	Reduced	56	56	
T1663	Ac-ATSLIHSIIIESQSQKNEQELLELDKWSLWVWF-NH2	Native			
T1664	Ac-YASLIHSIIIESQSQKNEQELLELDKWSLWVWF-NH2	Native			
T1665	Ac-YTALHSIIIESQSQKNEQELLELDKWSLWVWF-NH2	Native			
T1660	Ac-YTSAIHSIIIESQSQKNEQELLELDKWSLWVWF-NH2	Reduced			
T1661	Ac-YTSLAHSIIIESQSQKNEQELLELDKWSLWVWF-NH2	Reduced			
T1662	Ac-YTSLIASIIIESQSQKNEQELLELDKWSLWVWF-NH2	Native			
T1656	Ac-YTSLIHAIIESQSQKNEQELLELDKWSLWVWF-NH2	Native			
T1657	Ac-YTSLIHSIIIESQSQKNEQELLELDKWSLWVWF-NH2	Reduced			
T1659	Ac-YTSLIHSIIIESQSQKNEQELLELDKWSLWVWF-NH2	Inhibited			
T1653	Ac-YTSLIHSIIIESQQAEEAELLELDKWSLWVWF-NH2	Native			60
T1654	Ac-YTSLIHSIIIESQQAEEAELLELDKWSLWVWF-NH2	Native			
T1655	Ac-YTSLIHSIIIESQQAEEAELLELDKWSLWVWF-NH2	Inhibited			
T1650	Ac-YTSLIHSIIIESQQAEEAELLELDKWSLWVWF-NH2	Inhibited			1000
T1651	Ac-YTSLIHSIIIESQQAEEAELLELDKWSLWVWF-NH2	Native			14
T1652	Ac-YTSLIHSIIIESQQAEEAELLELDKWSLWVWF-NH2	Native			40
T1630	Ac-YTSLIHSIIIESQQAEEAELLELDKWSLWVWF-NH2	Inhibited			>1000
T1631	Ac-YTSLIHSIIIESQQAEEAELLELDKWSLWVWF-NH2	Reduced			200
T1632	Ac-YTSLIHSIIIESQQAEEAELLELDKWSLWVWF-NH2	Native			27
T1627	Ac-YTSLIHSIIIESQQAEEAELLELDKWSLWVWF-NH2	Native			27
T1628	Ac-YTSLIHSIIIESQQAEEAELLELDKWSLWVWF-NH2	Reduced			250
T1629	Ac-YTSLIHSIIIESQQAEEAELLELDKWSLWVWF-NH2	native			53

FIG. 54



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/35727

A. CLASSIFICATION OF SUBJECT MATTER IPC(7) :C12Q 1/70; G01N 33/53; A61K 38/00, 39/21 US CL :435/5, 7.1; 530/300; 424/188.1, 208.1 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : 435/5, 7.1; 530/300; 424/188.1, 208.1 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) USPATFUL, WPIDS, MEDLINE		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHEN, C.-H., et al., A Molecular Clasp in the Human Immunodeficiency Virus (HIV) Type 1 TM Protein Determines the Anti-HIV Activity of gp41 Derivatives: Implication for Viral Fusion. J. Virol. June 1995. Vol. 69. No. 6. pages 3771-3777, see entire document.	1-3
Y	US 5,656,480 A (WILD et al.) 12 August 1997, see entire document.	1-3
Y	US 5,464,933 A (BOLOGNESI et al.) 07 November, 1995, see entire document.	1-3
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* "A" "E" "L" "O" "P"	Special categories of cited documents: document defining the general state of the art which is not considered to be of particular relevance earlier document published on or after the international filing date document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) document referring to an oral disclosure, use, exhibition or other means document published prior to the international filing date but later than the priority date claimed	"T" "X" "Y" "&" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art document member of the same patent family
Date of the actual completion of the international search 04 JUNE 2001		Date of mailing of the international search report 25 JUNE 2001 (25.06.01)
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